

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

VANDA PHARMACEUTICALS,)
INC.,)
Plaintiff,) C.A. No. 18-651-CFC
v.)
TEVA PHARMACEUTICALS)
USA, INC., et al.,)
Defendants.)

Tuesday, March 29, 2022
9:04 a.m.
Bench Trial

Volume 2

844 King Street
Wilmington, Delaware

BEFORE: THE HONORABLE COLM F. CONNOLLY
United States District Court Judge

APPEARANCES:

MORRIS NICHOLS ARSHT & TUNNELL
BY: KAREN JACOBS, ESQ.
BY: DEREK J. FAHNESTOCK, ESQ.

-and-

1 APPEARANCES CONTINUED:

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P R O C E E D I N G S

1 (Proceedings commenced in the courtroom beginning at
2 9:04 a.m.)
3

4 **MS. JACOBS:** Your Honor, I just want to briefly
5 report on our efforts following your direction yesterday
6 with counsel that -- including the counsel you mentioned
7 yesterday. We did meet in person for about an hour last
8 night. We continued to correspond by e-mail, met some
9 more this morning. We have reached a number of agreements
10 which we're in the process of memorializing.

11 But just relevant for the upcoming
12 examinations, one thing I just want to make clear since
13 you won't be hearing it, is that we've agreed each expert
14 is qualified as an expert in the relevant field. So you
15 won't hear us offering or proffering experts as experts in
16 particular areas of expertise. Each expert has applied
17 the Court's claim construction, so you won't be hearing
18 about that.

19 We've also -- will be memorializing what the
20 disputed issues are as to particular claim limitations for
21 infringement. We reached agreement about what portions of
22 270, 271 are -- apply or are the issue in the case. So we
23 are memorializing that. But I just wanted to let you know
24 it was productive.

25 **THE COURT:** Right. And that's helpful. Let me

1 just comment on one thing. But it's good for me to hear
2 about the qualifications of experts, right. I mean, that
3 would be factored into my determination of their abilities
4 and credibility. So I'm not trying to say, don't do that,
5 right. I mean, but just as long as that clarification is
6 made from my end is understood.

7 **MS. JACOBS:** Yes, Your Honor. I think we have
8 that in mind as well. It would certainly be up to each
9 party to still give Your Honor the background, that would
10 be helpful. It's just that there need not be sort of a
11 background proffer in order to establish that someone is
12 an expert in the field.

13 **THE COURT:** Thank you. That was helpful. All
14 right.

15 **MR. GROOMBRIDGE:** And, Your Honor, Vanda's next
16 witness is Dr. Stephen Bergmeier.

17 **THE COURT:** All right.

18 **MR. GROOMBRIDGE:** And my colleague, Ms. Young,
19 will be presenting this witness.

20 **THE COURT:** All right.

21 **THE CLERK:** Please remain standing and raise
22 your hand. Please state and spell your name for the
23 record.

24 **THE WITNESS:** My name is Stephen Bergmeier.
25 S-T-E-P-H-E-N, B-E-R-G-M-E-I-E-R.

1 Stephen Bergmeier, having been called as a witness,
2 being first affirmed or duly sworn under oath, testified
3 as follows:

4 **THE WITNESS:** I so affirm.

5 **MS. YOUNG:** Good afternoon, Your Honor.
6 Josephine Young for Vanda.

7 Before we begin, I also wanted to mention that
8 the parties have come to an agreement that defendants
9 products infringe all of the elements of Claim 10 of the
10 '465 patent, except for the reducing step. So we will be
11 focusing on that in our presentation.

12 **THE COURT:** Okay.

13 **MR. ROZENDAAL:** Yes. The entire contacting and
14 the reacting step, that includes the reducing step, yes.

15 **THE COURT:** Okay. Thank you.

16 DIRECT EXAMINATION

17 **Q.** Dr. Bergeimer, please introduce yourself to the
18 Court.

19 **A.** My name is Stephen Bergmeier. I'm a professor and
20 chair of the department of chemistry and biochemistry at
21 Ohio University.

22 **Q.** What is your educational background?

23 **A.** I have a bachelor's degree in chemistry from Ohio
24 State University, a master's in organic chemistry from
25 University of Nebraska, and a PhD in medicinal chemistry

1 from the University of Michigan. And that was followed by
2 postdoctoral work at the University of California at
3 Berkeley.

4 **Q.** When did you do your postdoctoral work?

5 **A.** I'm sorry. Could you repeat that?

6 **Q.** When did you do your postdoctoral work?

7 **A.** I worked on the synthesis of a variety of compounds
8 that were potentially useful for the treatment of cancer.

9 **Q.** And when was that?

10 **A.** '91 to '93, I believe.

11 **Q.** And how long have you worked at Ohio University?

12 **A.** I've worked there since 2000.

13 **Q.** What is the focus of your research?

14 **A.** Focus of my research is the development of new
15 synthetic methods, as well as the design and synthesis of
16 small molecules that might be useful for the treatment of
17 Type 1 diabetes, treatment of cancer, and treatment of
18 infectious diseases.

19 **Q.** Does any of your research involve the identification
20 of compounds for which you don't know the structure?

21 **A.** We quite routinely do not know the structure of
22 compounds that have been made, and so we do a lot of work
23 at trying to identify those.

24 **Q.** Do you have any experience with developing
25 pharmaceutical compounds?

1 **A.** I worked at Warner-Lambert Parke-Davis for several
2 years. And in that capacity, I was developing new
3 antipsychotic drugs.

4 **Q.** Do you have any experience with identifying
5 impurities in pharmaceutical compounds?

6 **A.** Again, at Warner-Lambert Parke-Davis, that was a lot
7 of the job was to identify the impurities and make sure
8 that you had a pure compound.

9 **Q.** If you could turn in the white binder that we have in
10 front of you to the first tab, PTX- 822.

11 Do you recognize this document?

12 **A.** Yes, that's my CV.

13 **Q.** Did you prepare this CV?

14 **A.** Yes, I did.

15 **Q.** Is it accurate as of July 2021?

16 **A.** Yes, it is.

17 **Q.** Aside from any updates in your list of publications
18 and presentations, is it otherwise accurate?

19 **A.** Yes, it is.

20 **MS. YOUNG:** We'd like to offer PTX- 094 into
21 evidence.

22 **MR. ROZENDAAL:** No objection.

23 **THE COURT:** All right. It's admitted.

24 **MS. YOUNG:** PTX- 822. I'm sorry.

25 **MR. ROZENDAAL:** No objection to 822,

1 Your Honor.

2 **THE COURT:** Okay.

3 (PTX-822 is admitted into evidence.)

4 **BY MS. YOUNG:**

5 **Q.** Dr. Bergmeier, in this case, am I correct that you
6 have examined both infringement and validity issues?

7 **A.** Yes, I have.

8 **Q.** And is it your intention to return to this courtroom
9 to testify about validity after defendant's experts have
10 testified?

11 **A.** Yes, that is my plan.

12 **Q.** Today, we're going to confine our questions to the
13 topic of infringement, so let's start with the '465
14 patent.

15 Could you look in your binder to the document
16 behind --

17 **THE COURT:** So can I ask you a question?
18 Remember we want to sidebar yesterday?

19 **MS. YOUNG:** Yes.

20 **THE COURT:** And I asked you why are we talking
21 about all those topics. And the response was, because it
22 had to do with invalidity. So why did we hear that from
23 that witness yesterday, which was pretty lengthy about
24 invalidity, but we don't hear from this person?

25 **MS. YOUNG:** Your Honor, Mr. Pandrapragada was

1 talking about the invention and the work that led up to
2 the invention. It's not necessarily related to
3 infringement. But traditionally it is in the
4 case-in-chief, and I don't believe defendants had any
5 objections.

6 **THE COURT:** I was just asking about the --
7 well, they also didn't have the reaction I did, which is
8 what relevance it had.

9 **MS. YOUNG:** Yes. So in general, it doesn't --
10 his testimony did not have any relevance to infringement,
11 I agree, but it had relevance to what led up to the
12 invention and how the '465 came to be.

13 **THE COURT:** But why didn't you, then, for the
14 same reason you are having this expert wait and only
15 testify about infringement? Why didn't you do that with
16 the witness yesterday?

17 I'm asking this counsel.

18 **MR. GROOMBRIDGE:** I'm sorry, Your Honor.

19 **MS. YOUNG:** I'm sorry. Can you please repeat?

20 **THE COURT:** So why would you question that
21 witness about what you just said? It had nothing to do
22 with infringement.

23 So why did we do that in your case-in-chief
24 yesterday, as opposed to wait like you're going to do with
25 this witness and do invalidity when we do invalidity?

1 **MS. YOUNG:** I apologize, Your Honor. We had
2 just assumed that because it was about how the invention
3 came to be, and that's normally presented in the
4 case-in-chief, we assumed that it was appropriate to do it
5 at that time.

6 **THE COURT:** Okay.

7 **MS. YOUNG:** Also -- I'm sorry. Also, we had an
8 agreement with the other side that the examination could
9 go outside the scope of the infringement issues.

10 **THE COURT:** All right.

11 **BY MS. YOUNG:**

12 **Q.** So let's now turn to the '465 patent.

13 Could you look in your binder to the document behind
14 the tab labeled JTX- 006?

15 **A.** Yes.

16 **Q.** What is JTX- 006?

17 **A.** That is the '465 patent.

18 **Q.** In rendering your infringement opinions, did you
19 consider Claim 10 of the '465 patent?

20 **A.** Yes, I did.

21 **Q.** And on Slide 4 of PDX- 06, did you break down
22 Claim 10 into its elements, incorporating the language of
23 Claim 1 from which it depends?

24 **A.** Yes, I did.

25 **Q.** Just to orient us a bit, at a high level, what does

1 Claim 10 require?

2 **A.** It requires preparing tasimelteon by contacting and
3 reacting the carboxamide with reducing an acid -- agent
4 and an acid. And that's followed by contacting and
5 reacting the resulting methanamine with a propionylating
6 reagent to prepare the tasimelteon, again, where the
7 composition comprises 0.15 percent or less. Impurities 5,
8 6, 1, 2, and 3.

9 **Q.** And what kind of reaction is the first contacting and
10 reacting step?

11 **A.** We call it a reducing reaction or a reduction.

12 **Q.** And what kind of reaction is the second contacting
13 and reacting step?

14 **A.** I would call it an acylating step or we call it a
15 propionylating reagent, because we are just adding a
16 three-carbon piece.

17 **Q.** All right. And then focusing on the reducing step,
18 what kind of compound is the first chemical compound in
19 the reducing step?

20 **A.** We're taking a carboxamide.

21 **Q.** Is it okay if we call that the carboxamide, instead
22 of the full chemical name?

23 **A.** Yes. The full chemical name gives us the structure,
24 but we don't really need that for talking about it.

25 **Q.** Great.

1 And what kind of compound is the last chemical
2 compound in the reducing step?

3 **A.** The methanamine.

4 **Q.** And is it okay if we call that last compound the
5 methanamine?

6 **A.** Yes.

7 **Q.** Since there's a stipulation of infringement with
8 regard to the propionylating step in the impurities, let's
9 turn to the reducing step, which I believe we -- is on
10 Slide 5.

11 What does the reducing step require?

12 **A.** Requires that we take the carboxamide -- and we have
13 the structure there that corresponds with the name up
14 there. And we contact it and react it with a reducing
15 agent, followed by an acid in an organic solvent to
16 prepare the methanamine or a salt of the methanamine.

17 **Q.** In the reaction scheme that you have up on Slide 5,
18 what is being shown?

19 **A.** Basically, the overall general reaction reducing
20 agent, acid, and organic solvent.

21 **Q.** And what is shown on the right of the arrow?

22 **A.** That is our methanamine or the product of that
23 reaction.

24 **Q.** For the reducing step of Claim 10 of the '465 patent,
25 can the product also be a methanamine salt?

1 **A.** Yes, it can.

2 **Q.** Were you here for opening statements?

3 **A.** Yes, I was.

4 **Q.** Did you hear Mr. Coblentz's statement in his opening
5 that the reducing step of Claim 10 requires that the same
6 carboxamide chemical compound react with a reducing agent,
7 as well as the acid?

8 **A.** Yes, I did.

9 **Q.** Do you agree with that statement?

10 **A.** No, I do not.

11 **Q.** Why not?

12 **A.** Basically, taking a reducing agent and an acid in the
13 same -- at the same time would not effectively work. The
14 reducing agent would simply react with the acid and not
15 react with the --

16 **MR. ROZENDAAL:** Objection, Your Honor.

17 Undisclosed expert testimony.

18 **THE COURT:** Okay.

19 **MS. YOUNG:** He disclosed his claim construction
20 arguments in his opening infringement report.

21 **THE COURT:** Can you identify it for me? Hand
22 me up the report, please.

23 **MS. YOUNG:** Sure. With regard to Apotex, he
24 had disclosed it on -- in his August 27, 2021 report. On
25 Page 6 of Paragraph 18, he says the claim --

1 **THE COURT:** Just, can you give me a copy of the
2 report?

3 **MS. YOUNG:** I'm sorry.

4 Your Honor, it might take us a moment to find
5 the expert reports binder.

6 Do you mind if we move on to our next topic
7 while we resolve that issue?

8 **THE COURT:** Sure.

9 **MS. YOUNG:** I apologize.

10 **THE COURT:** That's all right. So what I should
11 do is then -- hold on.

12 **MR. ROZENDAAL:** Your Honor, we move to strike
13 the last answer.

14 **THE COURT:** Well, what I was going to do is
15 hold that in abeyance. We'll just hold it in abeyance if
16 you want to come back to it. Thanks.

17 **BY MS. YOUNG:**

18 **Q.** Dr. Bergmeier, do you understand that there are
19 essentially two defendants in this case, Teva and Apotex?

20 **A.** Yes, I do.

21 **Q.** When considering whether or not Teva and Apotex
22 infringed Claim 10 of the '465 patent, did you consider
23 them together or separately?

24 **A.** I considered them separately.

25 **Q.** Let's discuss Teva first. With regard to Teva, what

1 did you find as to whether or not they infringed Claim 10
2 of the '465 patent?

3 **A.** My opinion was that they did infringe. They
4 contacted and reacted the carboxamide with the reducing
5 agent and an acid to prepare the methanamine salt, and
6 subsequently contacted and reacted methanamine with like a
7 propionylating reagent to prepare tasimelteon.

8 **Q.** What about Apotex?

9 **A.** My opinion was, again, that Apotex infringes on
10 Claim 10. Their manufacturing process also contacts and
11 reacts the carboxamide with a reducing agent to prepare
12 the methanamine salt, and subsequently contacts and reacts
13 the methanamine with a propionylating reagent to prepare
14 tasimelteon.

15 **Q.** When coming to your opinions about what the reducing
16 step means and whether defendants infringe Claim 10 of the
17 '465 patent, did you consider who would be a person of
18 ordinary skill in the art?

19 **A.** My definition was simply a person having a bachelor's
20 degree in chemistry or organic chemistry or related
21 discipline.

22 **Q.** Are you a person of at least ordinary skill in the
23 art under your definition?

24 **A.** Yes.

25 **Q.** Do you understand that the defendants in this case

1 have an expert who has rendered opinions about
2 infringement and validity issues regarding Claim 10 of the
3 '465 patent?

4 **A.** Yes, I do.

5 **Q.** Who is that?

6 **A.** It's Dr. Robert Perni.

7 **Q.** Did Dr. Perni render an opinion as to who a person of
8 ordinary skill in the art would be for the '465 patent?

9 **A.** Yes, he did.

10 **Q.** Is Slide 9 his definition?

11 **A.** Yes, it is.

12 **Q.** Do you agree with Dr. Perni's definition of a person
13 of ordinary skill?

14 **A.** No, I do don't.

15 **Q.** As I understand that Dr. Perni's definition requires
16 a certain education and work experience, as well as
17 certain experience with regulatory considerations.

18 Taking the education and work requirement first, do
19 you agree with that aspect of Dr. Perni's definition?

20 **A.** No, I don't. I think someone with less experience or
21 education would meet that definition.

22 **MR. ROZENDAAL:** Your Honor, may we have a brief
23 sidebar?

24 **THE COURT:** Sure.

25 - - -

1 (Whereupon, the following discussion is held at
2 sidebar.)

3 **MR. ROZENDAAL:** I'm sorry to interrupt the
4 examination. I don't think that this disagreement about
5 the person of skill in the art is relevant to the
6 infringement issue. I think we can skip this for now, and
7 that if we end up having the fight, it will make more
8 sense in the context of the invalidity discussion.

9 **MR. GROOMBRIDGE:** I'm fine with that
10 understanding. If there's not going to be a challenge on
11 the infringement over this, that's fine with us. And it
12 may be that we, by the time of the validity case, we will
13 have worked it out.

14 **THE COURT:** Can I ask, because it comes up
15 generally -- I mean, in every case it comes up, in every
16 case. Does it come up on appeal? Where is it when it
17 become really relevant?

18 **MR. GROOMBRIDGE:** It rarely comes up on appeal.
19 Occasionally it does, and then it can have very serious
20 consequences.

21 As I'm sure Mr. Rozendaal is aware, there was a
22 recent case in which the Federal Circuit essentially threw
23 out the whole chunk of proof saying this person wasn't
24 qualified, and so it makes the trial lawyers sensitive to
25 the issue.

1 **THE COURT:** Did they raise it below or is it
2 one of those occasions where a brand-new argument was
3 raised on appeal? I don't understand if it doesn't come
4 up as an issue in trial how it would get properly
5 litigated on appeal.

6 **MR. GROOMBRIDGE:** I do not know. Your Honor,
7 it must have been preserved below the Federal Circuit
8 would have said forget it.

9 **THE COURT:** Not sure about that, but okay.

10 **MR. GROOMBRIDGE:** Maybe our views may differ or
11 experiences may differ.

12 **THE COURT:** Thank you for that suggestion and
13 the agreement of the parties. So I think we can move on
14 and save this for another day.

15 (Whereupon, the discussion at sidebar concludes.)

16 - - -

17 **BY MS. YOUNG:**

18 **Q.** So let's talk about Teva and whether -- Teva's
19 process.

20 In the binder in front of you, the next tab should be
21 labeled PTX-094.

22 Do you recognize this document?

23 **A.** Yes, I do.

24 **Q.** What is this document?

25 **A.** It's a description of the manufacturing process and

1 the process controls for Teva.

2 Q. And who is Zhejiang?

3 A. Oh, this is the -- I'm sorry. This is the report
4 from them to Teva describing the process that they are
5 using to manufacture tasimelteon for Teva.

6 Q. Did you consider PTX-094 in rendering your
7 infringement opinions?

8 A. Yes, I did.

9 MS. YOUNG: I'd like to offer PTX-094 into
10 evidence.

11 MR. ROZENDAAL: No objection.

12 THE COURT: It's admitted.

13 (PTX-094 admitted into evidence.)

14 BY MS. YOUNG:

15 Q. Have you created a demonstrative, Slide 11, that sets
16 forth Teva's manufacturing process?

17 A. Yes, I did.

18 Q. At a high level, what is Teva's manufacturing
19 process?

20 A. They start off with a compound called TSM1, carry it
21 through several chemical steps to ultimately generate the
22 carboxamide TSM7, which is then reduced to TSM8 and
23 subsequently converted to tasimelteon.

24 Q. Have you examined Teva's manufacturing process for --
25 to determine if it has the reducing step of Claim 10?

~~Bergmeister~~ - Direct

1 **A.** Yes, it does.

2 **Q.** Which step is it?

3 **A.** It's the step converting TSM7 to TSM8.

4 **Q.** Let's focus on that step on Slide 12.

5 How does that step in Teva's process compare to the
6 reducing step of Claim 10?

7 **A.** It does take a carboxamide. That's TSM7. Treats it
8 with a reducing agent -- in this case, it's a mixture of
9 BF3 etherate and sodium borohydride -- and then an acid to
10 generate the methanamine salt.

11 **Q.** What, then, did you conclude about whether Teva's
12 process met the reducing limitation of Claim 10?

13 **A.** It does meet those limitations. Again, it takes the
14 carboxamide with the reducing agent, then an acid and
15 organic solvent to prepare, in this case, the methanamine
16 salt.

17 **Q.** And so, now, let's switch gears and talk about
18 Apotex. And let's go back to the binder in front of you.
19 The next tab should be JTX-50.

20 Do you recognize JTX-50?

21 **A.** Yes, I do.

22 **Q.** What is JTX-50?

23 **A.** It's a description of the manufacturing process and
24 process controls for the synthesis of Apotex's tasimelteon
25 product.

~~Bergmeister~~ - Direct

1 Q. Did you consider JTX-50 in rendering your opinions?

2 A. Yes, I did.

3 MS. YOUNG: I'd like to offer JTX-50 into
4 evidence.

5 MR. COBLENTZ: No objection.

6 THE COURT: It's admitted.

7 (JTX-50 admitted into evidence.)

8 BY MS. YOUNG:

9 Q. I understand that you created a demonstrative on
10 Slide 15 that sets forth Apotex's manufacturing process.

11 A. Yes, I did.

12 Q. At a high level, what is Apotex's manufacturing
13 process?

14 A. So, again, they start off with a different starting
15 material. In this case, it is TAS10. Again, taking it
16 through several chemical steps, they arrive at the
17 carboxamide TAS50, which is then reduced to generate a
18 salt, TAS60, of the methanamine, and then propionylated to
19 prepare the tasimelteon product, or TAS.

20 Q. Have you examined Apotex's manufacturing process to
21 determine if it has the reducing step of Claim 10?

22 A. Yes, I did.

23 Q. And does it?

24 A. Yes, it does.

25 Q. Which step is it?

1 **A.** It's the conversion of TAS50 to TAS60.

2 **Q.** So let's focus on that step.

3 And on the next slide, Slide 16, how does that step
4 in Apotex's process compare to the reducing step of
5 Claim 10?

6 **A.** So they take the carboxamide TAS50, treat it with a
7 reducing agent -- in this case, it's sodium borohydride
8 and aluminum chloride in an organic solvent, and then
9 treated with an acid to generate the methanamine salt,
10 TAS60.

11 **Q.** In your opinion, does Apotex's step meet the reducing
12 claim limitation of Claim 10 of the '465 patent?

13 **A.** Yes, it does. It takes the carboxamide with a
14 reducing agent to prepare the methanamine salt.

15 **Q.** So what is your opinion as to whether or not Apotex's
16 generic tasimelteon product infringes Claim 10 of the '465
17 patent?

18 **A.** I would say yes, it does. It certainly meets that
19 claim.

20 **MS. YOUNG:** I think at this time, we're ready
21 to show Your Honor the expert reports that go to the issue
22 of claim construction.

23 **THE COURT:** Okay. Well, I hope they don't
24 because he's not supposed to be construing the claim,
25 right? When you say "go to the issue of claim

1 construction," what do you really mean?

2 **MS. YOUNG:** So I believe defendants and Vanda
3 have a claim construction dispute as to what the
4 contacting and reducing step means to a person of ordinary
5 skill in the art. And we had not presented to the Court
6 because we had understood that the Court would prefer to
7 hear these claim construction issues at trial.

8 **THE COURT:** I don't remember that. So can you
9 all, I mean --

10 **MR. ROZENDAAL:** I'm not sure that I recall the
11 claim construction issue, Your Honor. I think Your Honor
12 said plain and ordinary meaning. And we think that the
13 plain and ordinary meaning is clear, but --

14 **MS. YOUNG:** I don't believe the Court has ever
15 ruled on the meaning of this claim and whether or not it
16 has the plain and ordinary meaning.

17 **THE COURT:** All right. So your position is I
18 deferred claim construction on this?

19 **MS. YOUNG:** You had deferred claim construction
20 on a patent related -- related to the '465 patent with
21 regard to the '977 patent. I don't know if the Court
22 recalls that the parties had a dispute about whether or
23 not the preset specifications and the order of certain
24 claim terms needed to be construed. And you had
25 instructed that you would prefer to hear claim

1 construction issues at trial since it was a bench trial.

2 **THE COURT:** Okay.

3 **MS. YOUNG:** As I result, we did not present
4 this claim construction issue as another wave of claim
5 construction disputes for you to hear at a Markman
6 hearing. We reserved it for trial.

7 **MR. ROZENDAAL:** To be clear, I don't think the
8 patent was in suit at the time of the Markman hearing, and
9 certainly the issue of claim construction for this term
10 has never been raised to us in the course of the case
11 leading up to now.

12 **MS. YOUNG:** Vanda respectfully disagrees
13 because it was presented in the expert reports.

14 **MR. STONE:** The only thing I would add, Your
15 Honor -- Eric Stone -- this patent didn't exist at the
16 time of Markman. And the dispute between the parties is
17 when it says "contacting it with this and that," does it
18 mean at the same time sequentially or either of those
19 things?

20 And essentially it's a dispute about the word
21 "and."

22 **MR. ROZENDAAL:** Well, no, again, I don't agree
23 with that characterization either, Your Honor. The claim
24 term says "contacting and reacting a carboxamide with a
25 reducing agent." And everybody agrees that that means

1 that the reducing agent needs to contact and react with
2 the carboxamide. The result -- and then in the processes
3 that we're talking about now, that happens. And then the
4 carboxamide is gone and there's a methanamine. And in the
5 process we're talking about, the methanamine is contacted
6 with the acid afterwards. And as a result, the acid does
7 not contact and react with the carboxamide.

8 That is our noninfringement position.

9 And I understand Vanda to be taking the
10 position, essentially, that it doesn't matter; that when
11 it says "contacting and reacting the carboxamide with the
12 acid," it doesn't mean that. It means contacting and
13 reacting the product of the reaction and the carboxamide
14 with the reducing agent in an acid. And we just don't
15 think that's what the claim says.

16 **THE COURT:** Okay. All right.

17 I had a claim construction hearing on
18 October --

19 **MS. YOUNG:** It is the August --

20 **THE COURT:** Sorry.

21 I had a claim construction hearing, I believe,
22 on October 10, 2019; is that right?

23 **MR. GROOMBRIDGE:** I believe so, Your Honor.

24 **THE COURT:** Did I have any other claim
25 construction hearings?

1 **MR. ROZENDAAL:** No, I don't believe.

2 **MS. YOUNG:** So on August 19, 2020, there was a
3 discussion about scheduling claim construction hearing.

4 **THE COURT:** Okay.

5 **MS. YOUNG:** And it was at that hearing that you
6 had provided some guidance as to how we should proceed.

7 **THE COURT:** Okay. Do you have a transcript of
8 that hearing?

9 **MS. YOUNG:** I have my own copy that is
10 highlighted.

11 **THE COURT:** Well, hold on a second.

12 Ms. Young, were you present at the October 2019
13 claim construction hearing?

14 **MS. YOUNG:** I was not present, Your Honor.

15 **THE COURT:** Have you reviewed it? Do you know
16 if this issue came up at all then?

17 **MS. YOUNG:** It did not, Your Honor.

18 **THE COURT:** Okay. So because it's patented, it
19 exists, then?

20 **MS. YOUNG:** That's correct.

21 **THE COURT:** All right. But you've mentioned
22 there is a similar patent or at least a patent that has
23 similar claim language?

24 **MS. YOUNG:** That's right. It's the parent of
25 this patent.

1 **THE COURT:** Was that parent in dispute when I
2 had the Markman hearing in October 2019?

3 **MS. YOUNG:** It was, Your Honor.

4 **THE COURT:** Okay.

5 **MR. ROZENDAAL:** But it doesn't have the same
6 limitation, Your Honor.

7 **THE COURT:** That was going to be my next
8 question.

9 So was this limitation, or language that
10 approximates this limitation, brought to my attention in
11 connection with the October of 2019 claim construction
12 hearing?

13 **MS. YOUNG:** No, Your Honor.

14 **THE COURT:** Okay. So the first time this was
15 raised, I am gathering, was in August of 2020.

16 **MS. YOUNG:** That's correct, Your Honor. We had
17 a secondary dispute about the claim terms in the '977
18 patents. Again, it is not related to the reducing step,
19 but it was an additional claim construction dispute that
20 the parties had, and it was at that time you had provided
21 us guidance as to whether or not you wanted separate
22 Markman or to present testimony at trial.

23 **MR. ROZENDAAL:** But, Your Honor, the patent was
24 not in existence as of August 2020 either. It didn't
25 issue until November of 2020.

1 **THE COURT:** All right. Hold on a second.

2 **MS. YOUNG:** I mean, if it would be helpful at
3 all, the guidance I am referring to is on Page 42 of the
4 transcript.

5 **THE COURT:** I'm reading that page, and what I
6 am quoted as saying is that -- first of all, let me step
7 back.

8 I think that in the October of 2019 hearing,
9 there was at least one term where I said, effectively,
10 let's have a bench -- I mean, why not hear from the
11 experts at the bench trial, right? And I think it would
12 boil down to you had essentially disputes about the plain
13 and ordinary meaning of terms. And I said, look, rather
14 than have a hearing, it is a bench trial; I can deal with
15 it then. Right?

16 **MS. YOUNG:** That's correct.

17 **THE COURT:** All right.

18 **MR. ROZENDAAL:** I believe that was the
19 seven-to-nine-hour issue.

20 **THE COURT:** It could be. But I just -- as I
21 said, it is at least one term. I remember that. I
22 skimmed the claim construction transcript recently about
23 the entrainment issue, which even back then was kind of
24 "the issue" it seems to me. Right? It's going to be "the
25 issue" on appeal. All right.

1 Now, on page -- then you come to me -- this
2 August conference, I have to go back and look at the
3 beginning of the transcript. But it seems to me to be
4 there might have been some discovery, some scheduling
5 disputes.

6 It was not a claim construction. It was not --
7 the purpose of the conference was, I didn't think, to
8 address claim construction. Is that right?

9 **MS. YOUNG:** I believe the purpose of the
10 conference was to discuss discovery disputes that arose
11 because of claim construction disputes.

12 **THE COURT:** Okay.

13 **MS. YOUNG:** And so towards the end, there was a
14 discussion about whether or not there should be a
15 scheduling of the claim construction conference. And
16 that's when --

17 **THE COURT:** Well, here's what I said. First of
18 all, I was recalling what had happened in the October
19 hearing of 2019. And Mr. Warner said something to the
20 effect that he thought resolution of some of these issues
21 would be reached -- that the parties would go forward with
22 the case and they would resolve some of these disputes at
23 trial.

24 And then I said -- I would slightly rephrase
25 the way you stated it. And I said, quote: My

1 recollection is this is just really boiling down to a
2 battle of the experts, and whether you couch it as claim
3 construction or final opinions about validity or
4 infringement, it's really is a battle of experts. So why
5 not save it all for a bench trial?

6 That seems to still be, you know, a smart,
7 efficient way to proceed, in my mind. So to the extent
8 you expect at the Markman hearing that I'm going to
9 really -- in order to decide what highly purified
10 tasimelteon means in Claim 22, I'm really going to resort
11 to expert, it seems to me. You know, why not save it all
12 for trial.

13 So my statement, at least there, seems to be
14 very specific. It's with respect to Claim 22 and, in
15 particular, with what the meaning of "highly purified
16 tasimelteon" means.

17 Is that even an issue still?

18 **MS. YOUNG:** No.

19 **THE COURT:** That's why you should never rule
20 before a trial because it doesn't mean anything. All
21 right. But at least I'm not saying there that I'm going
22 to hear claim construction about this term.

23 Now, that's not to say we shouldn't hear it.
24 But as I'm listening to this gentleman testify and looking
25 at the language that's posted on Slide 6.17, it does seem

1 to me that we've got a claim construction issue here or an
2 interpretation of the claim.

3 **MS. YOUNG:** That's correct, Your Honor.

4 **THE COURT:** All right. That's your position.
5 Okay.

6 And your position, Mr. Rozendaal?

7 **MR. ROZENDAAL:** Well, I don't want to split
8 hairs about whether it is or isn't a claim construction
9 issue. I think we have a reading of the claim in which
10 the acid has to contact the carboxamide or react -- and
11 react with the carboxamide.

12 **THE COURT:** Yep.

13 **MR. ROZENDAAL:** And I think what we're hearing
14 is testimony that that doesn't happen.

15 **THE COURT:** Agreed. That's what I heard.

16 **MR. ROZENDAAL:** That doesn't happen in the
17 accused products. And they, essentially, want to say,
18 well, what that really means is not that the carboxamide
19 contacts and reacts with the acid, but that the product of
20 the reduction of the carboxamide contacts and reacts with
21 the acid.

22 **THE WITNESS:** The product being the methanamine
23 or the salt thereof.

24 **MR. ROZENDAAL:** Correct. Well, the methanamine
25 reacts with the acid, yes.

1 **THE COURT:** Okay.

2 **MR. ROZENDAAL:** And I just don't think there's
3 any dispute that that doesn't -- sorry, that -- I don't
4 think there's any dispute that there is a reduction in the
5 carboxamide to the methanamine before the acid enters the
6 picture, and that's why we say we don't infringe.

7 **THE COURT:** All right. Okay.

8 **MR. ROZENDAAL:** And you call that a claim
9 construction dispute or you call that a --

10 **THE COURT:** Right. And that's what your expert
11 just testified to, correct?

12 **MS. YOUNG:** That's correct.

13 Our position is that the plain and ordinary
14 meaning of this claim, as an organic chemist would
15 understand it, would be that it's very standard for a
16 reduction reaction to be written as contacting with a
17 reducing agent and an acid, and understand that the acid
18 as afterwards as a --

19 **THE COURT:** Okay. So actually --

20 **MR. ROZENDAAL:** None of that is in his expert
21 report, Your Honor.

22 **MS. YOUNG:** We respectfully disagree.

23 **THE COURT:** Okay. Well, then, first of all, I
24 will look at his expert report.

25 Do you have it?

~~Bergmeier~~ - Direct

1 **MS. YOUNG:** Yes, I do.

2 **THE COURT:** Which one and where?

3 **MS. YOUNG:** If you start with PTX-772, I
4 believe, is Apotex's -- Dr. Bergmeier's opening report
5 with regard to Apotex.

6 **THE COURT:** Okay. What page?

7 **MS. YOUNG:** And if you go to Page 6,
8 Paragraph 18, about halfway down says: The claim
9 limitation does not specify when the reducing agent, acid,
10 organic solvent, or other components are introduced into
11 the reaction, whether simultaneously, sequentially, or
12 otherwise.

13 And then it follows further down: Because the
14 claim language is silent as to order of addition of
15 reagents, a person of ordinary skill in the art would not
16 understand that the claims required any particular order.

17 **THE COURT:** I mean, why doesn't that address
18 it?

19 **MR. ROZENDAAL:** Because that's not what he --
20 that's not what he was testifying to, Your Honor. If he
21 wants to say exactly those words, that's fine, but he went
22 well -- he was well beyond that.

23 **MS. YOUNG:** And if you can turn --

24 **THE COURT:** Well, hold up. Hold up. Let me
25 just...

1 **MS. YOUNG:** I'm sorry.

2 **THE COURT:** Go ahead.

3 **MR. ROZENDAAL:** It's one thing to say that you
4 can add the acid to the mixture first or the reducing
5 agent to the mixture first; that's one thing. That's what
6 I read this to be saying. It's a different thing to be
7 saying the acid never has to contact the carboxamide.

8 If they wanted to write a claim --

9 **THE COURT:** Hold up. Hold up.

10 Did we have a sidebar before or after this
11 question was first posed and put on hold?

12 **MR. STONE:** I believe it was after.

13 **THE COURT:** The sidebar was after?

14 **MR. STONE:** I believe it was.

15 **THE COURT:** I'm looking at the rough transcript
16 at Page 28 or 29, Lines 21. And we -- the court reporter
17 used a shorthand, so I don't have the exact question as --
18 it's something to the effect: Did you hear Mr. Coblantz's
19 statement in his opening that the reducing step in
20 Claim 10 requires that the same carboxamide chemical
21 reagent with reducing agent as well as the agents I had --
22 I'm sure that's a shorthand.

23 What was your question? See, you write your
24 questions out so you should just go --

25 **MS. YOUNG:** Yeah.

1 Did you hear Mr. Coblentz's statement in his
2 opening that the reducing step of Claim 10 requires that
3 the same carboxamide chemical compound reacts with the
4 reducing agent and the acid?

5 **MR. STONE:** I think it's actually the next
6 question, Your Honor.

7 **MS. YOUNG:** Oh, is it the next question?

8 **THE COURT:** All right. Then basically taking a
9 reducing agent and an acid at the same time.

10 Right, that's the question you were asking
11 next?

12 **MS. YOUNG:** I think it was how would a person
13 of ordinary skill in the art understand the phrase
14 "contacting and reacting to some things with a reducing
15 agent acid in an organic solvent."

16 **MR. ROZENDAAL:** I think the question was why
17 not.

18 **MS. YOUNG:** Oh, I'm sorry. Oh.

19 **MR. ROZENDAAL:** The --

20 **THE COURT:** Hold on a second.

21 **MR. ROZENDAAL:** Sure.

22 **THE COURT:** That's not the question I have at
23 all.

24 **MS. YOUNG:** I apologize. I thought I had
25 gotten further in my outline. I apologize.

1 **THE COURT:** But I think Mr. Rozendaal was
2 anticipating where you were going.

3 **MR. ROZENDAAL:** I'm not sure I am looking at
4 the same point in the transcript, Your Honor. But it
5 says:

6 Did you hear Mr. Coblentz say this?

7 Yes, I did.

8 Do you agree with it?

9 No, I do not.

10 Why not?

11 That's the part that's not in the report.

12 **THE COURT:** Oh. And then his answer is what's
13 followed. Okay. All right. It's a question -- all
14 right. I see. Gotcha.

15 All right. I don't know how the court reporter
16 gets half of this stuff down, let alone as much as she
17 does. It's so difficult. All right. Okay.

18 All right. Well, look, I agree. If the point
19 is if he's trying to explain, as it looks like he was,
20 that taking the reducing agent and the acid at the same
21 time would not effectively work. That's not in PDX-772,
22 Paragraph 18. I agree with that. It's not.

23 Okay. Do you want to point me to somewhere else?

24 **MS. YOUNG:** So if you can look at --

25 **THE COURT:** Now, mind you, what you haven't

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1 asked him is this -- to discuss this opinion on Page 18 --
2 in Paragraph 18, I should say, which goes, really, to
3 claim construction.

4 **MS. YOUNG:** Right.

5 **THE COURT:** Okay. But anyway, go ahead. You
6 want to show me something else?

7 **MS. YOUNG:** Yes, if you could go to PTX-795,
8 which is Dr. Bergmeier's reply.

9 **THE COURT:** All right.

10 **MS. YOUNG:** It's on Page 28, Paragraph 8.

11 **MR. ROZENDAAL:** May we have just a moment to
12 find that, Your Honor?

13 **THE COURT:** Yes, I need a moment, too.

14 All right. Page 28, paragraph what?

15 **MS. YOUNG:** Sixty-eight.

16 **THE COURT:** All right. Let me just read it.

17 **MS. YOUNG:** Sure.

18 **THE COURT:** The last line seems to me, Mr.
19 Rozendaal, to potentially allow for this testimony. I
20 don't want to say it in front of the witness. If you
21 want, we can have a sidebar.

22 **MR. ROZENDAAL:** If we could, Your Honor,
23 please.

24 **THE COURT:** Let's do a sidebar.

25 - - -

1 (Whereupon, the following discussion is held at
2 sidebar.)
3

4 **THE COURT:** I mean, the last sentence refers to
5 the yield, which is implicit in his answer in the
6 transcript was talking about the effectiveness of the
7 reactions. I mean, is there some -- maybe there's some
8 difference.

9 **MR. ROZENDAAL:** I think there is a difference.
10 I think what he says here at Paragraph 68 is it wouldn't
11 be a very smart way to do it, to put them in together
12 because the yield would be low. It would be kind of not
13 an efficient way to do it.

14 What he started to say here is that if you put
15 the acid in first, the reaction won't work.

16 **THE COURT:** Well, he said the word -- maybe he
17 is going to say that, but --

18 **MR. ROZENDAAL:** I guess the point is that he
19 has not -- well, I don't think the fight is about whether
20 one could or could not add the reagents in a particular
21 order; the question is whether regardless of what the
22 reagents are --

23 **THE COURT:** When you say "reagents" --

24 **MR. ROZENDAAL:** I mean reducing agent and the
25 acid.

1 **THE COURT:** Let's hold up. I do think this is
2 going to be claim construction is my reaction.

3 Do we all agree that reagents include the
4 reducing agent and the acid?

5 ALL COUNSEL: Yes.

6 **THE COURT:** Now, is an organic solvent a
7 reagent?

8 **MR. ROZENDAAL:** I don't think we would say
9 that, Your Honor.

10 **MR. GROOMBRIDGE:** No.

11 **THE COURT:** So you agree on that. All right.

12 So this seems to me to be essentially, you
13 know, I'm going to diagram the sentence. That's really
14 what it's going to boil down to. It's my call, and so I'm
15 going to let the testimony in. We will see what happens.
16 I mean, if it starts to be something way beyond the yield,
17 then I think there's a problem.

18 Like, for instance, if he all of a sudden said
19 that this reaction would be impossible, I don't know how
20 he could have that opinion since he's talking about a
21 yield. A yield implicitly means there was some product.
22 So if he were to say that this chemical reaction is not
23 possible, I wouldn't find it credible.

24 And in that regard, maybe you should let it in.
25 He's talking about a yield. There has to be a reaction.

1 What do you anticipate he's going to say?

2 **MS. YOUNG:** I don't anticipate. I anticipate
3 him to say that a person of ordinary skill would
4 understand normally. This reduction is done by adding the
5 reducing agent and then quenching with an acid. That is
6 the sequence of events. There's no implication that --

7 **THE COURT:** That goes to Paragraph 18. If he
8 testified to that, I don't think there's an objection to
9 that.

10 **MS. YOUNG:** I was trying to set up the context
11 from the opening statement. We understand there was a
12 claim construction dispute.

13 **MR. ROZENDAAL:** To be clear, though, what
14 counsel has just proffered is a situation in which the
15 acid does not contact the carboxamide. When you talk
16 about quenching, you are not talking about reacting with
17 the carboxamide. The quenching, as I understand it, is
18 using up the excess reducing agent. So whatever the
19 quenching is doing is not --

20 **THE COURT:** Quenching is a --

21 **MR. ROZENDAAL:** -- one for me. Hold on.

22 **MR. GROOMBRIDGE:** Your Honor, we think this is
23 primarily a claim construction dispute. And we think
24 that -- and we touched on this last night. We did not
25 reach agreement about it. We think that it will fall to

1 Your Honor. But it might be helpful for the Court to have
2 the benefit of hearing from both experts.

3 **THE COURT:** I want to hear from them. Believe
4 me, I will hear from them. That's why I said let it in.

5 I'm saying I understand why Mr. Rozendaal made
6 the objection, because the answer started to sound like it
7 wasn't going to be limited to the optimization of the
8 yield, right. It sounded like it might say something much
9 broader.

10 On the other hand, frankly, if he had said
11 that, it would have been. Like I said, certainly cast
12 questions in my mind about his credibility, given what the
13 statement says about yield in the report.

14 So I kind of think let's let it in. And so I
15 will deny the motion to strike. Let's hear it, and
16 then -- at least right now, though, certainly where I am,
17 is this is going to boil down to how I read this language
18 in the claim.

19 **MR. GROOMBRIDGE:** Your Honor, we are positing
20 the best way to do it would be to address claim
21 construction issue in post-trial briefing, whatever form
22 that helps Your Honor to make out the arguments.

23 **THE COURT:** I may not have to wait that long.
24 And partly, I do want to hear -- I would want to hear
25 expert testimony before I made a claim construction in

1 this. I'm not sure we have to brief it. It's not -- that
2 seems to me it's pretty easy in the sense that there's
3 some language there. To the extent there's ambiguity, I'm
4 going to hear from two experts. And I don't think I need
5 briefing to decide that one. We'll see.

6 Unless you are going to tell me -- the only
7 thing I'm troubled by, this was not raised in that
8 August 2020 conference, right, the patent hadn't issued
9 yet. Was this raised -- when was this put before me, that
10 I had a claim construction issue like this?

11 **MR. GROOMBRIDGE:** I think the first time that
12 we realized this was turning into a claim construction
13 dispute was when we heard the opening yesterday.

14 **THE COURT:** Okay.

15 **MR. ROZENDAAL:** I think -- well, I think our
16 position on this was pretty clearly set forth in our
17 expert reports, Your Honor. I'm surprised to hear that
18 that --

19 **THE COURT:** We'll see. The bottom line is, we
20 have the ability to resolve the issue. Okay. So I'm
21 going to deny the motion to strike, but -- and let the
22 questioning proceed and see what comes out. Thank you.

23 **BY MS. YOUNG:**

24 **Q.** Dr. Bergmeier, returning to the issue of what the
25 compounding and reacting stuff --

1 (Reporter clarification.)

2 **MS. YOUNG:** I apologize.

3 **BY MS. YOUNG:**

4 **Q.** Dr. Bergmeier, returning to the -- what the reducing
5 step means on Slide 5 of PDX- 6, how would a person of
6 ordinary skill in the art understand the phrase
7 "contacting and reacting something with a reducing agent
8 in an acid in organic solvent in terms of sequence."

9 **MR. ROZENDAAL:** Objection.

10 **THE COURT:** So that is a different question.
11 But here's the thing, if I were going to have a -- I'm
12 going to need to have a Markman hearing, right? So why
13 not just have a Markman hearing, and I will let the expert
14 evidence come in. I'm going to let your expert respond,
15 okay. I mean, at the end of the day, it is a question of
16 law. If I have to, I could under 02 Micro say, let's have
17 a Markman hearing right now. Right?

18 **MR. ROZENDAAL:** You could do that or --

19 **THE COURT:** I'm not sure how much weight -- I
20 will say that question is not in the report.

21 **MS. YOUNG:** Okay. Well, let me -- sorry. Let
22 me get the report in front of me.

23 **THE COURT:** It wasn't in the paragraph I
24 identified. The paragraph we discussed at sidebar was
25 pretty specific.

1 **MS. YOUNG:** Should I -- I apologize,
2 Your Honor. Should I reask the question prior to the
3 motion to strike, or should I just start with the claim
4 construction question?

5 **THE COURT:** Well, I kind of don't know where
6 this question is going now, is the problem. See, I mean,
7 why don't you start with the question that you were posing
8 at the time that there was an objection by Mr. Rozendaal.

9 **MS. YOUNG:** Great.

10 **BY MS. YOUNG:**

11 **Q.** Did you hear -- Dr. Bergmeier, did you hear
12 Mr. Coblentz's statement in his opening that the reducing
13 step of Claim 10 requires the same carboxamide chemical
14 compound to react with the reducing agent and the acid?

15 **A.** Yes, I did.

16 **Q.** Do you agree with that statement?

17 **A.** No, I do not.

18 **Q.** Why not?

19 **A.** When I read that statement in the claim, I basically
20 apply what I know about chemistry, and know that I would
21 first add a reducing agent, and then I would follow that
22 with an acid.

23 **Q.** Do you agree that -- would you -- what is your
24 opinion as to whether or not the claim language suggests
25 that the reducing agent and acid both react with the

1 carboxamide compound?

2 **A.** My opinion is they don't and that they probably
3 can't.

4 **Q.** But why is that?

5 **MR. ROZENDAAL:** Objection, Your Honor.
6 Undisclosed testimony.

7 **THE COURT:** Well, I kind of agree. But let's
8 just hear the answer, then you can -- I'm not ruling on
9 your objection.

10 **BY MS. YOUNG:**

11 **Q.** Why is that?

12 **A.** I guess there are multiple reasons. From a purely
13 chemical perspective, there are reagents that react
14 together, and so we would not mix them together.

15 From a "I want to carry out this procedure myself"
16 perspective, I would go into the body of the patent and
17 look at the method, which is actually spelled out as to
18 how that reaction is actually carried out, and which --
19 you know, I read the '465 patent. They treat it with a
20 reducing agent and then they add an acid.

21 **MS. YOUNG:** And, Mr. Weir, if you could pull up
22 JTX- 006 at Page 8, Column 13.

23 **MR. ROZENDAAL:** Again, I'm going to renew the
24 motion to strike.

25 **THE COURT:** Well, hold on. So he didn't give

1 the answer that I think you thought, right, and he
2 referred to the embodiment. He did discuss this
3 embodiment in his report, I'm pretty sure. And so I'm
4 going to let him go ahead and talk about it.

5 **MS. YOUNG:** Mr. Weir, if you could blow up
6 Column 13, starting around Line 32, to the end of the
7 Scheme 5.

8 **BY MS. YOUNG:**

9 **Q.** Is this the section you were describing,
10 Dr. Bergeimer?

11 **A.** Yes, I am -- yes, it is. Sorry.

12 **Q.** And what is being described there?

13 **A.** This is the reduction step, where they take the
14 carboxamide -- they're calling it Intermediate 4 here --
15 treating it. As you look at the reaction over the arrow
16 there, you've got the reducing agent, in this case it's
17 lithium aluminum hydride, in an organic solvent. That's
18 the THF. And then there's Step 2. Underneath the arrow
19 there is our acid, HCL.

20 And when I read the description, they say lithium
21 aluminum hydride and an organic solvent, followed by an
22 aqueous workup and isolation of the resulting amine as its
23 hydrochloride salt.

24 **Q.** There is the little compound that is being reduced,
25 contact both the reducing agent and the acid at the same

1 time?

2 **A.** No, it does not.

3 **Q.** What follows this portion of the specification?

4 **A.** I believe the much more detailed description of how
5 the reaction is carried out follows this, sort of
6 abstract, if you will.

7 **Q.** And in that specific example, does the carboxamide
8 react with the reducing agent, which then reacts with the
9 acid to form the methanamine salt, or methanamine salt
10 thereof, I mean? Or does it literally say that the
11 carboxamide compound has to react with the reducing agent
12 and the acid?

13 **A.** No. I mean, the majority of the description is how
14 the lithium aluminum hydride, or the reducing agent,
15 reacts with the carboxamide, and then it finishes up with
16 adding an acid.

17 **Q.** Other than this reducing-step disclosure in this
18 section of the patent, are there any other examples of a
19 reducing step in the '465 patent?

20 **A.** I do not believe that there are.

21 **Q.** Based on how a person of ordinary skill in the art
22 would understand the reducing step, and in light of the
23 claim language and how the specification describes the
24 reducing step, what is your view as to what is required
25 for the reducing step of Claim 10?

Bergmeier - Cross

1 **A.** My view is that the carboxamide will react with the
2 reducing agent, and the resulting product of that
3 reduction step is a reaction with some type of acid.

4 **Q.** Based on that understanding of the claim limitations
5 for the reducing step, would Teva's -- would Teva infringe
6 Claim 10 of the '465 patent?

7 **A.** My opinion is that, yes, that it does.

8 **Q.** And based on that understanding of the claim
9 construction, would Apotex infringe Claim 10 of the '465
10 patent?

11 **A.** My opinion is that they would, yes.

12 **Q.** What would be the effect on yield if the acid were
13 added at the same time as the reducing agent?

14 **A.** I would say that your yield would be negligible, as
15 the acid would react with the reducing agent from the very
16 beginning and essentially remove it from the reaction
17 process.

18 **MS. YOUNG:** I have no further questions at this
19 time.

20 **THE COURT:** All right. Thank you.

21 **MR. ROZENDAAL:** May I cross?

22 CROSS EXAMINATION

23 **BY MR. ROZENDAAL:**

24 **Q.** Do you have a black binder from us, Doctor?

25 **A.** I have one. Thank you.

Bergmeier - Cross

1 Q. Good morning. I am a J.C. Rozendaal. I don't think
2 we've met yet, but --

3 A. No.

4 Q. Let's take a look, please -- turn in your binder, if
5 you would, to JTX- 50, which is one of the documents you
6 spoke about on direct. It's already in evidence, so we
7 can pull it up on the screen. Here we go.

8 And this is the Apotex manufacturing process, right?

9 A. Yes, it is.

10 Q. And you testified on direct that the Apotex process
11 contains the particular carboxamide intermediate that's
12 mentioned in Claim 1 of the '465 patent, right?

13 A. Yes.

14 Q. And that is identified in JTX- 50 as TAS-50; is that
15 correct?

16 A. Yes.

17 Q. And you also testified that in the acid in the Apotex
18 manufacturing process corresponds -- that corresponds to
19 the acid in Claim 1 is hydrochloric acid; is that right?

20 A. Yes.

21 Q. Okay. And we agree, don't we, that in the Apotex
22 process, the carboxamide is first reduced to a methanamine
23 in one step of the reaction, and only after that reduction
24 reaction is complete, the HCL is added; is that right?

25 A. Yes, it is.

1 Q. All right. And the same thing is true of Teva,
2 right? You said --

3 MR. ROZENDAAL: And, actually, we can take that
4 down.

5 BY MR. ROZENDAAL:

6 Q. If we go to PTX- 94, which is also in evidence, this
7 is the Teva reaction document. Can we please go to Page 2
8 of the document.

9 And you testified that the manufacturing process for
10 Teva's product also has the particular carboxamide
11 intermediate mentioned in Claim 1 of the '465 patent; is
12 that right?

13 A. Yes.

14 Q. And in Teva's process documents, the carboxamide is
15 referred to as TSM-7?

16 A. Yes.

17 Q. And then -- and the -- you also testified that the
18 acid in Teva's process that corresponds to acid in Claim 1
19 is hydrochloric acid; is that correct?

20 A. Yes, it is.

21 Q. And in Teva's process, the carboxamide is first
22 reduced to methanamine, and then only after that reduction
23 reaction is complete, is the HCL added?

24 A. Yes.

25 Q. And so we agree, then, that in this set of reaction

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1 steps, the hydrochloric acid is not contacting and
2 reacting with the carboxamide, it's contacting and
3 reacting with the methanamine?

4 **A.** That is correct.

5 **MR. ROZENDAAL:** No further questions,
6 Your Honor.

7 **THE COURT:** Redirect?

8 **MS. YOUNG:** None, Your Honor.

9 **THE COURT:** All right. Before you step down,
10 may I ask you a few questions?

11 **THE WITNESS:** Yes, Your Honor.

12 **THE COURT:** Can we put up JTX- 50, please. Can
13 we blow up, doesn't matter which one. Let's pick like the
14 one -- the big -- there, that one right there. You've got
15 it. Let's blow that up.

16 You see where I have this arrow right here?

17 **THE WITNESS:** Yes.

18 **THE COURT:** What does the arrow mean to an
19 artisan of ordinary skill?

20 **THE WITNESS:** That you're going to transform
21 the molecule before the arrow into the molecule after the
22 arrow.

23 **THE COURT:** All right. Now, I notice that in
24 various documents that have been put before me, including
25 the patent and including this document, they've got things

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1 that are above the arrow and things that are below the
2 arrow.

3 **THE WITNESS:** Yes.

4 **THE COURT:** Is there a significance to being
5 put above or below the arrow?

6 **THE WITNESS:** No, it's really where it fits.

7 **THE COURT:** What do you mean by that?

8 **THE WITNESS:** If you're just -- it's just --

9 **THE COURT:** You mean where it fits on the page?

10 **THE WITNESS:** Yes.

11 **THE COURT:** Just aesthetics?

12 **THE WITNESS:** Yes.

13 **THE COURT:** So you could have all of them
14 above, all of them below, it doesn't matter?

15 **THE WITNESS:** No.

16 **THE COURT:** Okay. Now, and it lists various
17 things. In this particular example, which is right next
18 to TAS-60, there are nine different things listed.

19 **THE WITNESS:** Yes.

20 **THE COURT:** All right. What are those nine
21 things?

22 **THE WITNESS:** So here --

23 **THE COURT:** Just give me a definition. I'm
24 using the word "things" as Joe Sixpack, right? You give
25 me the definition for -- as an artisan of ordinary skill,

1 what are those things?

2 **THE WITNESS:** They are individual, sort of,
3 transformations or things that one has to do.

4 So, for example, the very bottom one, there is
5 dry. And so most of the time, you might not put that dry
6 in there. But here, you know, for their method of, sort
7 of, the preparation of the larger quantity, they are going
8 to list every single little step.

9 But a normal artisan, someone skilled in the
10 art wouldn't necessarily put dry or something like that,
11 because you would know that, oh, when I get done with
12 this, I'm going to remove the solvent and dry my product.

13 **THE COURT:** All right. So dry sounds like a
14 verb, right?

15 **THE WITNESS:** Yeah.

16 **THE COURT:** All right. So it is to do
17 something?

18 **THE WITNESS:** Yes.

19 **THE COURT:** But sometimes they list -- and the
20 reason why I use "things," because it almost seems, in my
21 experience, most of the times they're listing a noun.

22 **THE WITNESS:** Right.

23 **THE COURT:** They are listing a molecule or a
24 compound or something.

25 **THE WITNESS:** Most of the time, you're listing

1 a reagent that you're going to add to the reaction.

2 **THE COURT:** Right. And that doesn't have a
3 verb. It doesn't say add the reagent. It just has the
4 name of the reagent?

5 **THE WITNESS:** Yes.

6 **THE COURT:** All right. What's a "reagent"?

7 **THE WITNESS:** It could be anything. So on the
8 very top line, we have sodium borohydride and aluminum
9 chloride. That's our reducing reagent. Under the next --

10 **THE COURT:** Well, is aluminum chloride, is that
11 a reagent in this particular example?

12 **THE WITNESS:** Yes. Yes, it is.

13 **THE COURT:** Okay. Is it fair that -- to draw
14 the inference that anytime that there is a chemical or
15 molecule or a noun that is identified above or below the
16 transformation arrow --

17 **THE WITNESS:** Right.

18 **THE COURT:** -- it is a reagent?

19 **THE WITNESS:** Well, if it's a noun, it's not
20 really a -- I would not call it a reagent.

21 **THE COURT:** Well, I would have said sodium
22 hydrochloride is a noun.

23 **THE WITNESS:** So --

24 **THE COURT:** So we can get on the same page just
25 grammatically, what's a noun to you?

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1 **THE WITNESS:** Yeah. I'm sorry. A verb.

2 Sorry.

3 **THE COURT:** Okay. Yeah. So clearly, it is a
4 verb. Dry is not a reagent.

5 **THE WITNESS:** Right. But a noun --

6 **THE COURT:** My question is, if it's a noun, if
7 it's aluminum -- so is aluminum chloride a reagent?

8 **THE WITNESS:** Yes, it is.

9 **THE COURT:** Now, again, heat could be a noun or
10 verb, but I am assuming it's a verb there, right?

11 **THE WITNESS:** Yes.

12 **THE COURT:** So hydrochloric acid, is that a
13 reagent in this reaction?

14 **THE WITNESS:** Yes, it is. Yes, it is.

15 **THE COURT:** So basically, any chemical, any
16 molecule is going to be a reagent; is that fair?

17 **THE WITNESS:** Pretty much. You know, they
18 list, on that top line, diethyl and tetrahydrofuran. They
19 are solvents. And some people would call them reagent,
20 some people not. That's sort of a matter of semantics
21 there. But it is something that's added into the
22 reaction, or it's part of the actual reaction.

23 **THE COURT:** So a solvent, you would say, is not
24 a reagent?

25 **THE WITNESS:** No.

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1 **THE COURT:** Well, that was a negative on my
2 part.

3 Is a solvent a reagent?

4 **THE WITNESS:** I would not consider it a
5 reagent.

6 **THE COURT:** So, then, that's an example of a
7 noun that could be listed above or below the arrow that
8 does not qualify as a reagent?

9 **THE WITNESS:** Yes.

10 **THE COURT:** All right. Is there a rule that
11 you could give me, that if I were to go look at one of
12 these schematics for a chemical reaction with the arrow,
13 that I -- I could then interpret whether something is a
14 reagent or not a reagent that's a noun?

15 **THE WITNESS:** Umm.

16 **THE COURT:** So, for instance, rule one would
17 be, it sounds like, except solvents, right?

18 **THE WITNESS:** Right.

19 **THE COURT:** Okay. Are there any other rules?

20 **THE WITNESS:** No, not really.

21 **THE COURT:** Okay. So it's either a reagent or
22 a solvent if it's a noun.

23 **THE WITNESS:** Right.

24 **THE COURT:** Okay. All right. And the last
25 question I have for you is, when you were asked some

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1 questions about claim construction and about the yield,
2 you were asked a specific question about the yield.

3 Do you recall the question?

4 **THE WITNESS:** Yes.

5 **THE COURT:** What do you recall the question
6 was?

7 **THE WITNESS:** If you added the acid and the
8 reducing agent at the same time, what would the yield be.

9 **THE COURT:** Right.

10 **THE WITNESS:** And I said it would be negligible
11 because the acid and the reducing agent would kind of
12 cancel each other out.

13 **THE COURT:** So in your expert report, you wrote
14 that -- the other side's interpretation of that
15 limitation, right, you said it's contrary because it
16 would, quote, have a negative impact on the yield of the
17 methanamine, right?

18 **THE WITNESS:** Right.

19 **THE COURT:** You didn't say it was going to be
20 negligible, did you?

21 **THE WITNESS:** I did not say negligible.

22 **THE COURT:** All right. Thank you.

23 **THE WITNESS:** Okay.

24 **THE COURT:** You may step down.

25 All right. Next.

~~Bergmeier~~

1 **MR. STONE:** Your Honor, at this time, Vanda
2 rests its case-in-chief.

3 **THE COURT:** Okay. Great.
4 Defendants.

5 **MR. ROZENDAAL:** Your Honor, we would move for a
6 judgment of noninfringement on partial findings for
7 Claim 3 of the RE604 patent, for Claim 14 of the '829
8 patent, Claim 4 of the '910 patent, and Claim 10 of the
9 '465 patent.

10 In particular, with regard to the RE604 patent,
11 which is the entraining patent, we think it's been clear
12 that the plaintiffs have failed to establish that a
13 physician reading the label -- or rather, that the label
14 instructs a physician to carry out the various steps
15 mentioned in the preamble, the entraining, the
16 maintaining, the seven-to-nine hours, et cetera, and that,
17 for that reason, they have failed to meet their burden of
18 proof on infringement.

19 With regard to the '829 and '910 patents, which
20 are the CYP inducer and CYP inhibitor patents, we have a
21 similar situation.

22 It's our position that the relevant portions of
23 the label for inducement of infringement are the
24 indications and usage section and the dosage and
25 administration section. The indications and usage tells

1 you what to use the product for, and the dosage
2 administration tells you how to use it.

3 And unless one of those sections
4 cross-references some other part of the label, we don't
5 think it's appropriate for the Court to consider the other
6 parts of the label in deciding what the label instructs
7 physicians to do.

8 For that reason, because there's no mention of
9 any CYP or cross-reference, as one sometimes finds in
10 the -- in these sort of labels, because that's absent from
11 this label, we don't think that they have -- that the
12 plaintiffs have established active inducement of the CYP
13 limitations.

14 Moreover, even if one were to consider the
15 drug-drug interaction portion of the label, the language
16 there does not event a specific intent to cause physicians
17 to discontinue usage of CYP1A2 inhibitors or CYP3A4
18 inducers of rifampicin. Rather, the warning in that
19 portion of the label could be satisfied by simply
20 refraining from administering tasimelteon, rather than
21 discontinuing the use of the other drug.

22 And, again, that would be the HCNP case that
23 we've cited on -- in other words, if the label is
24 indifferent between one of two courses, then that is not
25 sufficient. If one of which is infringing and one of

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1 which is not infringing, that is not sufficient for an
2 active inducement of infringement.

3 And with regard to the product-by-process
4 patent, which we've just been talking about, I think
5 Your Honor understands our position because we've now
6 received unequivocal testimony that the acid does not
7 contact the carboxamide, but only contacts the
8 methanamine. I should say, contacts and react with the
9 methanamine; it does not contact or react with the
10 carboxamide.

11 For that reason, we think that there is no
12 infringement in either of the accused processes for the
13 '465 patent.

14 And we would propose to put in a short paper
15 memorializing these arguments for the Court later today,
16 if that --

17 **THE COURT:** I have no objection to that, but
18 you don't have to do that. All right.

19 **MR. GROOMBRIDGE:** Your Honor, do you wish to
20 hear a response?

21 **THE COURT:** Yeah, just brief. In the middle of
22 a bench trial, but I'm interested.

23 **MR. GROOMBRIDGE:** Your Honor, on the reissue
24 '604 patent and the entraining limitation, Vanda has
25 submitted plenty of evidence that a physician reading this

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1 label would understand it to be referring to entraining,
2 even though the word is not there.

3 We did follow up with the Court's questions
4 yesterday. And perhaps ironically, in our view, maybe the
5 most relevant cases, the prior Vanda case in which there
6 was a question about genotyping, which was -- the word --
7 term "genotyping" was in the claim, but not in the label.
8 This Court found infringement and the Federal Circuit
9 affirmed.

10 So we know from that that one absolutely can
11 have induced infringement as a method of treatment claim,
12 even when the word in the claim is not in the label.

13 **THE COURT:** Was that issue actually discussed
14 in the opinions, either in the District Court or the
15 Federal Circuit?

16 **MR. GROOMBRIDGE:** Yes, it was, Your Honor.
17 And, in fact, in the District Court, we tried the issue.
18 The label said --

19 **THE COURT:** What was the name of this case?

20 **MR. GROOMBRIDGE:** No, it's the --

21 **THE COURT:** What's the cite and the name of the
22 case?

23 **MR. GROOMBRIDGE:** It's Vanda versus -- I think
24 it's Westwood Pharmaceutical. Westwood. The name changed
25 over time. The citation in the Federal Circuit is 887

1 F.3d 1117.

2 **THE COURT:** Okay.

3 **MR. GROOMBRIDGE:** And in this Court, an issue
4 that actually was tried and ultimately decided by
5 Judge Sleet was when the label said tests are available,
6 the patent said use it -- genotype the patient, the
7 question was whether that label language meant genotyping
8 or not.

9 There was an elaborate debate at trial, and the
10 Court eventually ruled that that's how it would be
11 understood.

12 **THE COURT:** Okay.

13 **MR. GROOMBRIDGE:** And the Federal Circuit
14 affirmed.

15 So that's our view on the entraining issue
16 here.

17 On the two method-of-treatment patents, the
18 question -- the two drug-drug interaction patents, we
19 believe that it's -- or the position laid out by
20 defendants that only certain portions of the label may be
21 considered is incorrect as a matter of law. And there
22 are, indeed, Federal Circuit cases. I can't give the
23 Court the citation.

24 But, for example, the -- I believe the *Sanofi*
25 *versus Watson* case, which I think is 2017 in the Federal

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1 Circuit, actually talks about a reference to the clinical
2 trial section of the label in finding inducement of the
3 method-of-treatment claim, and we can certainly drill into
4 that if it be useful for the Court.

5 **THE COURT:** Okay.

6 **MR. GROOMBRIDGE:** And on the '465 patent we had
7 discussed at sidebar, in our view this is -- as it has now
8 emerged and the issue has truly been joined, it is a claim
9 construction issue. We think that it -- certainly the
10 testimony of the experts as to how a person of ordinary
11 skill would understand it is relevant. But ultimately,
12 there are other things in play, too.

13 I think Your Honor heard from Dr. Bergmeier's
14 testimony that the construction that is advocated by the
15 defendants would exclude the sole embodiment of the
16 patent. And, of course, there's a body of law around
17 things like that. It can happen, but it is a very rare
18 occurrence.

19 So in our view, the way to proceed -- we
20 certainly oppose the motion. We think that their claim
21 construction is erroneous, and we think that under our
22 claim construction, the facts are undisputed and there
23 would be infringement.

24 **THE COURT:** Is there anything else, besides the
25 testimony of your expert, which would be extrinsic

1 evidence, and could only be considered if I thought the
2 intrinsic evidence was adequate, right, to construe the
3 claim? Right?

4 **MR. GROOMBRIDGE:** Yes. *Teva versus Sanders*,
5 exactly.

6 **THE COURT:** So, then, I look at the intrinsic
7 evidence, and I obviously start with the claim language.
8 We haven't had argument about the grammar, but we can have
9 that.

10 But then there's an embodiment that is
11 consistent, you can argue, with your -- it seems to me it
12 is consistent with the way you read the claim. I'm not so
13 sure it is inconsistent with the way they do. But your
14 position would be that their reading of the claim would
15 read out that single embodiment.

16 **MR. GROOMBRIDGE:** Exactly. We would have a
17 claim that covers nothing that's in the patent.

18 **THE COURT:** Okay. Is there any other evidence
19 in the intrinsic record that, i.e., in the written
20 description, the pictures, the schemes, or the prosecution
21 history, that supports your claim construction?

22 **MR. GROOMBRIDGE:** There's none that's in my
23 mind as I stand here right now, Your Honor, because this
24 is -- at least the joining of the issue has been
25 relatively recent. I think we have not necessarily gone

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1 back through the file history and things like that to
2 look.

3 But Your Honor actually asked questions of
4 Dr. Bergmeier about, what does the arrow mean, what does
5 it mean when things are above it and below it, that in our
6 view are relevant, and it may be relevant to hear also
7 from defendants' expert --

8 **THE COURT:** Oh, I definitely want to hear from
9 the defendants. And I'm not going to -- I'm going to
10 reserve ruling. But what I do want you to do is, I want
11 you to confirm today if there's anything else in the
12 intrinsic record of this patent that you would cite in
13 support of your construction of the claim.

14 The other thing I want you to do is put to
15 any -- your position is going to be what, that it's -- are
16 you going to stick with plain and ordinary meaning, or do
17 you want to offer a construction of the claim?

18 **MR. GROOMBRIDGE:** The way I -- I mean, in my
19 mind, Your Honor, the way I thought of it is this is the
20 way a person of ordinary skill would read this claim, so I
21 think that is plain and ordinary meaning.

22 **THE COURT:** Okay.

23 **MR. ROZENDAAL:** But I haven't gone back and --

24 **THE COURT:** Well, it might be helpful, then,
25 for you to reword, just so you can tee up for me what the

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1 nub of the dispute is between the two parties. It might
2 be helpful. You clearly have different interpretations of
3 it and --

4 **MR. GROOMBRIDGE:** We certainly do. And I
5 think, without wanting to be presumptuous, but if this
6 question were posed to me, I would want both sides to have
7 laid out past the structure of the claim, right, and say,
8 how do you read that, right. There are other alternative
9 ways that it could be read. And also to look at the
10 intrinsic evidence and --

11 **THE COURT:** Right. But here's the reality. I
12 don't want to have -- to leave this week without deciding
13 this. Okay?

14 And the reason why is, and for the benefit of
15 the Federal Circuit, you know, I'm averaging, you know,
16 30-plus Markmans a year that actually go to hearing. I
17 mean, I'm preparing for more.

18 The way I function best is when I dive into the
19 patents and the technology and then I try to make a
20 decision so that I can move on to the next thing.

21 I've got all this fresh in my mind. I don't
22 want to lose this opportunity to construe the claim now.
23 Because I don't think it's that challenging in the sense
24 of mastering lots of information, right? It's giving it
25 time and attention and hearing from the lawyers.

~~Bergmeier~~

1 So we ought to do that this week.

2 **MR. GROOMBRIDGE:** Exactly, Your Honor. And all
3 the resources that we might need are here.

4 **THE COURT:** Correct. So we can't leave this
5 week without construing that claim. That's going to be
6 the goal.

7 So however you want. You've got a huge team.
8 I mean, my gosh, lots of lawyers in this room. We need to
9 get working on that.

10 **MR. GROOMBRIDGE:** Yeah.

11 **THE COURT:** All right. So I'm going to defer,
12 Mr. Rozendaal.

13 **MR. ROZENDAAL:** May I make a response?

14 **THE COURT:** Yes, please.

15 **MR. ROZENDAAL:** So I guess I would point out,
16 first of all, just to be clear, because I was treating it
17 rather in shorthand. But on this point, there is -- I
18 would point Your Honor to the *Chef America versus Lamb*
19 *Weston* case, which is 358 F.3d 1371 in the Federal Circuit
20 from 2004. And in that case -- it was a case for
21 industrial baking of cookies. And the cookie dough was
22 placed in an oven, and the embodiment in the claim was
23 that it was baked at a temperature of 400 to 800 degrees
24 Fahrenheit.

25 And then when they went to write the claim,

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1 instead of saying "baking the dough at a temperature of
2 800 degrees," the claim said "baking the dough to a
3 temperature of 800 degrees," which everyone agreed would
4 have turned it into a charcoal briquet.

5 And the Federal Circuit said, you know what,
6 that's what the claim says.

7 **THE COURT:** Right.

8 **MR. ROZENDAAL:** And so, therefore, I think this
9 is a very highly analogous situation.

10 **THE COURT:** Well, it could be. The problem --
11 the two is a little bit more unequivocal than some of the
12 language in this claim.

13 However, I need to read it, I need to think
14 about it, and you might be right. And definitely I am a
15 huge believer in, you live with your claims.

16 **MR. ROZENDAAL:** They wrote the claim. They
17 could have written it differently.

18 **THE COURT:** Somebody -- who was it? I just had
19 an inventorship case. Ms. Jacobs was in it last week. So
20 she heard me. She prevailed precisely because I said that
21 her adversary had to live with the claims that they wrote.

22 So yes, I get it.

23 **MR. ROZENDAAL:** And then just briefly on the
24 entrainment issue, I think the evidence has been clear
25 that the effects of tasimelteon sometimes entrain and

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1 sometimes treat by improving sleep outcomes.

2 And, again, that goes to a point similar to the
3 point we made for the CYP patents. If the result of the
4 instruction is one of two things, one of which would
5 infringe and one of which doesn't, that's not a
6 sufficient, specific intent to induce infringement.

7 I just wanted to clarify that.

8 **THE COURT:** Well, the legal issue, frankly, is
9 new to me. The factual issue, I don't think there's any
10 question that the plaintiff's expert said what you just
11 did. That's clear. I don't know enough about the law to
12 draw the legal conclusions, so I'm going to defer ruling.

13 **MR. ROZENDAAL:** Thank you, Your Honor.

14 **THE COURT:** Let's take a break for the court
15 reporter's benefit about 10 minutes.

16 Thank you.

17 **THE CLERK:** All rise.

18 (Whereupon, a recess was taken.)

19 **THE COURT:** Next.

20 **MR. LUKAS:** Yes, Your Honor. Defendants call
21 Ms. Deborah Jascot.

22 **THE COURT:** All right.

23 **MR. LUKAS:** May we approach with binders?

24 **THE COURT:** Sure.

25 DEBORAH JASKOT, having been called as a witness,

~~Jaskot~~ - Direct

1 being first affirmed or first duly sworn under oath,
2 testified as follows:

3 DIRECT EXAMINATION

4 **BY MR. LUKAS:**

5 **Q.** Good morning, Ms. Jaskot.

6 **A.** Good morning.

7 **MR. LUKAS:** And as I believe it was discussed
8 earlier today, Your Honor, there has been an agreement not
9 to challenge the expert's credentials. Ms. Jaskot is an
10 expert in FDA regulatory law and the drug approval process
11 behind that, but we will briefly go through some of her
12 background.

13 **THE COURT:** Sure.

14 **BY MR. LUKAS:**

15 **Q.** Ms. Jaskot, do you have a binder in front of you?

16 **A.** Yes.

17 **Q.** If you could, please, turn to the exhibit in that
18 binder marked DTX-399.

19 Do you recognize this document?

20 **A.** Yes. It's my CV.

21 **MR. LUKAS:** Your Honor, defendants move DTX-399
22 into evidence.

23 **MR. STONE:** No objection, Your Honor.

24 **THE COURT:** All right. It's admitted.

25 (DTX-399 admitted into evidence.)

~~Jaskot~~ - Direct

1 **BY MR. LUKAS:**

2 **Q.** Ms. Jaskot, if we could go to Page 2, and the bottom
3 of Page 2 specifically, what is your current title and
4 position?

5 **A.** Currently, for almost the past 10 years, I'm an
6 independent pharmaceutical consultant providing regulatory
7 advice to a broad range of clients: From virtual
8 companies to large branded companies.

9 **Q.** And prior to your work as an independent consultant,
10 what was your work experience prior to that?

11 **A.** After I finished --

12 **Q.** If you could turn back to Page 1.

13 **A.** After I finished my master's degree, I was working at
14 Cord Laboratories in 1986. Cord eventually became Sandoz,
15 and my position was drug regulatory affairs coordinator.

16 After that, I went to Teva in 1989, and I started
17 there as a regulatory affairs associate and moved up
18 through a series of more senior positions, all regulatory
19 affairs. And my last position was vice president of US
20 generic regulatory affairs and North America policy.

21 **Q.** Did you work during your time at Teva on regulatory
22 submissions related to any branded drugs?

23 **A.** Yes, although -- excuse me, predominantly generics.
24 There were branded drugs as well because Teva had acquired
25 NDAs for Azilect for the treatment of Parkinson's disease.

1 We also had Galzin for the treatment of Wilson's disease.
2 And my organization submitted the applications for
3 Copaxone for the treatment of multiple sclerosis. We
4 submitted applications to the US and Canada and ushered
5 them through to approval, including the negotiations on
6 the labels.

7 **Q.** Okay. And during the last eight years of your work
8 at Teva, what were your primary roles and
9 responsibilities?

10 **A.** I mainly monitored regulations, policy to determine
11 the impact to Teva's North American business branded and
12 generics. I supervised a staff of 140 regulatory
13 professionals at three different sites. And over the
14 course of my career, I've ushered through approval of
15 hundreds of applications.

16 **Q.** And in your positions at Teva, did you work closely
17 with FDA?

18 **A.** Yes, I was the primary liaison between Teva and the
19 FDA, especially the Office of Generic Drugs and the Office
20 of Pharmaceutical Science.

21 **Q.** And as part of your position and responsibilities at
22 Teva, were you responsible for reviewing marketing
23 materials for Teva's products?

24 **A.** Yes, routinely.

25 **Q.** And was your job to ensure that those marketing

1 materials complied with FDA regulations?

2 **A.** Yes, before they were used.

3 **Q.** And just before we move on, did any of your work at
4 Teva involve the drug at issue here, which is tasimelteon?

5 **A.** No, it did not.

6 **Q.** Did you prepare some demonstratives to assist with
7 your testimony today?

8 **A.** Yes, I did.

9 **MR. LUKAS:** Mr. Brooks, if we could, please,
10 bring up DDX-2.1.

11 **BY MR. LUKAS:**

12 **Q.** What does this demonstrative relate to as far as your
13 testimony today, Ms. Jaskot?

14 **A.** This is a general graphic of the FDA-mediated drug
15 approval process. It starts with the drug discovery and
16 preclinical R&D and moves on through to Phase 4, which is
17 post-approval.

18 The significant steps along the process are flagged.
19 The first step is the pre-IND. An IND is submitted after
20 the drug discovery and preclinical R&D.

21 **Q.** And at what point in this process does a sponsor of a
22 new drug typically select an indication to seek FDA
23 approval for?

24 **A.** It's typically before the IND is prepared.

25 **Q.** And what is the purpose of the IND?

1 **A.** It's short for Investigational New Drug application,
2 and that document contains all of the data that's been
3 collected from the drug discovery and preclinical phase.
4 And it's presented to FDA in order to get clearance to do
5 the first dose of the drug in humans.

6 **Q.** And would that be the Phase 1, Phase 2, Phase 3 that
7 we see here?

8 **A.** Yes, it is.

9 **Q.** During the process of the drug development and the
10 FDA review, are there meetings between a drug sponsor and
11 FDA?

12 **A.** Yes. FDA avail themselves of several key meetings.
13 The most important meeting, I would say, is the EOP2, end
14 of Phase 2 meeting. This is the meeting that occurs after
15 the Phase 2 trials are completed. And it's mainly for the
16 purpose of discussing the proposed indication, the style
17 of the Phase 3 studies, and the clinical endpoints to be
18 used to support the indication.

19 **Q.** Right. So at the end of Phase 2, that is -- is that
20 typically when the clinical endpoints are decided?

21 **A.** Yes.

22 **Q.** And is there typically agreement between the FDA and
23 a drug sponsor on the clinical endpoints that will be
24 used?

25 **A.** Typically, yes.

~~Jaskot~~ - Direct

1 Q. Did you prepare a demonstrative discussing clinical
2 endpoints that may be relevant to FDA approval?

3 A. Yes, I did.

4 MR. LUKAS: If we could go to DDX-2.2,
5 Mr. Brooks.

6 BY MR. LUKAS:

7 Q. What are the clinical endpoints described on this
8 slide?

9 A. These are the main clinical endpoints.

10 The primary endpoint is measurable results that can
11 be relied on to demonstrate a clinical benefit. And the
12 clinical benefit is something that favorably impacts the
13 patient's function, feelings, and survival.

14 The secondary endpoint is supportive information. By
15 itself, it does not support FDA approval, but it just can
16 be supportive.

17 A surrogate endpoint is a substitute for measuring an
18 actual clinical benefit. With extensive data, you can
19 establish that it correlates with the benefit.

20 Q. Now, in your review of -- did you review the NDA or
21 some of the NDA documents for Hetlioz?

22 A. Yes, I did.

23 Q. And during the application process for the drug that
24 became Hetlioz, was Vanda proposing the use of a surrogate
25 endpoint?

~~Jaskot~~ - Direct

1 **A.** Yes. They were proposing entrainment via the
2 measurement of the melatonin metabolite, as well as
3 urinary cortisol.

4 **Q.** Right. And did the FDA ever agree with the adoption
5 of a surrogate endpoint?

6 **A.** No. After numerous attempts to get FDA agreement,
7 agreement was never reached.

8 **Q.** And did you review some of the correspondence related
9 to the discussion of those surrogate endpoints?

10 **A.** Yes, I did.

11 **MR. LUKAS:** If we could go to DDX-2.3, please.

12 **BY MR. LUKAS:**

13 **Q.** Is this some of the correspondence you reviewed?

14 **A.** Yes.

15 **Q.** And on your timeline here, it looks like the first
16 document -- what is the first document?

17 **A.** The first document is the January 6, 2011 meeting
18 minutes from the end of Phase 2 meeting that was held
19 between Vanda and FDA.

20 **Q.** And is that document JTX-66?

21 **A.** Yes.

22 **Q.** And you reviewed that document in forming your
23 opinions?

24 **A.** I'm sorry?

25 **Q.** You reviewed that document in forming your opinions?

1 **A.** Yes, I did.

2 **MR. LUKAS:** Defendants move JTX-66 into
3 evidence, Your Honor.

4 **MR. STONE:** No objection, Your Honor.

5 **THE COURT:** It's admitted.

6 (JTX-66 admitted into evidence.)

7 **MR. LUKAS:** If we could, please, bring up
8 JTX-66, Mr. Brooks.

9 **BY MR. LUKAS:**

10 **Q.** Generally speaking, Ms. Jaskot, what is the format
11 and content of this document?

12 **A.** Typically, the sponsor will present to FDA questions
13 that they need answers to in order to continue on in their
14 development, and the FDA responds. This particular
15 document is FDA memorializing those questions and
16 responses in terms of meeting minutes.

17 **Q.** Right. And if we can turn to Page 3, and
18 specifically there's a first question there.

19 What was Vanda questioning FDA on here?

20 **A.** They were looking for an agreement on the two
21 studies, the 3201 and 3203 study, and they asked if these
22 studies were capable of supporting an indication for
23 tasimelteon.

24 **Q.** And what was the FDA's response?

25 **A.** They said no, we do not agree.

~~Jaskot~~ - Direct

1 Q. And just to be clear, what is the 3201 and 3203
2 studies that are referred to here?

3 A. 3201 study was a double-blind placebo-controlled
4 trial to establish efficacy; and the 3203 trial was a
5 continuation and open -- well, unblinded continuation to
6 establish the durability of the response.

7 Q. Right. And do you recall what the endpoints were
8 that Vanda was proposing to FDA for those studies at this
9 time?

10 A. At this time for the 3201, they were proposing total
11 nighttime sleep; and for 3203, they were proposing the
12 metabolite-based entrainment surrogate endpoint.

13 Q. And if we turn to Page 4 of JTX-66 at Question 5, is
14 there a discussion here of the use of a surrogate efficacy
15 biomarker?

16 A. Yes. FDA felt that -- well, there's two parts. For
17 the 3201 study, they felt that the total night's sleep was
18 not specific enough to establish a clinical benefit; and
19 for the 3203, they said they were skeptical that the
20 biomarkers are not well-enough understood in the disease.

21 Q. Was there also a discussion of possible other
22 clinical endpoints to be used?

23 A. Yes. They said that there appears to be -- the use
24 of clinically meaningful endpoints would be appropriate,
25 straightforward, and entirely possible.

~~Jaskot~~ - Direct

1 Q. Right. And if we turn to Page 5 of this document, in
2 the second full paragraph at the meeting between Vanda and
3 FDA, was there a discussion of the possible use of
4 clinically meaningful endpoints?

5 A. They discussed endpoints. And at some point, at
6 least FDA believed, that there was agreement -- and this
7 is at the bottom of that paragraph -- there's agreement
8 that nighttime sleep and daytime naps were the two most
9 important measures of clinical benefit.

10 Q. Now, turning back to DDX-2.3, in 2011 did Vanda adopt
11 the use of those endpoints?

12 A. No, they did not.

13 Q. JTX-66 is the next document in your timeline. What
14 is that document? Sorry, document 68. I'm sorry, I
15 misread that.

16 A. That's a document from FDA dated August 18, 2011, and
17 it is a letter responding to Vanda's request for a special
18 protocol assessment.

19 Q. And what is a "special protocol assessment,"
20 Ms. Jaskot?

21 A. You have the opportunity, prior to starting your
22 clinical trials, to submit your protocols to get an FDA
23 read on --

24 THE COURT: So we are not on the same page.
25 I've got JTX-68 being a document that's dated

1 October 2011.

2 **THE WITNESS:** It's temporally backwards; the
3 response is in the back. Almost all the way to the back.

4 **MR. LUKAS:** And I believe she's going to be
5 discussing the letter from August that begins on Page 57,
6 Your Honor. We were just about to get to that.

7 **THE COURT:** Just so you know, here's what the
8 transcript reflects.

9 I don't know what it is.

10 So you combined the question and the answer.
11 Did you get that?

12 But basically you say, JTX, the next document
13 in the timeline, was it that document? Sorry, document
14 68. Sorry I misread it.

15 Then the witness said, but she didn't answer;
16 that's a document dated August 18, 2011, and it is a
17 letter responding --

18 What I'm saying is when I look at JTX-68 --

19 **MR. LUKAS:** Yeah, it starts in October is what
20 you are saying?

21 **THE COURT:** Well, the first page is a document
22 dated October 13th. So maybe this has multiple documents
23 in there, you are saying?

24 **MR. LUKAS:** I am, and she was going to explain
25 that.

~~Jaskot~~ - Direct

1 **THE COURT:** Just for the record, since we'll
2 have to write an opinion after this data, if you could
3 clarify all of that, that would be great.

4 **MR. LUKAS:** We absolutely will, Your Honor.

5 **BY MR. LUKAS:**

6 **Q.** Was this document, JTX-68, something you reviewed in
7 forming your opinions?

8 **A.** Yes, it was.

9 **MR. LUKAS:** And defendants move JTX-68 into
10 evidence.

11 **MR. STONE:** No objection, Your Honor.

12 **MR. LUKAS:** Okay. Mr. Brooks, if we can please
13 bring JTX-68.

14 **THE COURT:** All right. It's admitted.

15 (JTX-68 admitted into evidence.)

16 **BY MR. LUKAS:**

17 **Q.** What is the format and content of this document,
18 Ms. Jaskot?

19 **A.** This, too, is a question-and-answer format, and it's
20 questions posed by the SPA and FDA's responses.

21 **Q.** Right. And in the front section of this document --
22 this is actually dated October. What is the front section
23 of the document, JTX-68?

24 **A.** As I understand, it was produced this way. I wanted
25 to switch it, but I wasn't permitted to.

~~Jasket - Direct~~

1 The front document is then a meeting that Vanda
2 requested of FDA, as a result of the protocol assessment.

3 **Q.** Okay. So is it your understanding that the front
4 part of the document is a response to the back part of the
5 document?

6 **A.** Yes.

7 **Q.** Okay. And if we could turn to the back part of the
8 document at Page 57.

9 Is this the August letter that you are referring to
10 as the SPA?

11 **A.** Yes, it is.

12 **Q.** And what is the format and content of this section of
13 the JTX-68?

14 **A.** This shows in the question-and-answer format.

15 **Q.** And if we turn to Page 57, what is the first question
16 being posed to FDA?

17 **A.** Vanda is asking: Does the division agree that the
18 statistically significant difference in entrainment for
19 study 3203, in combination with a statistically
20 significant improvement in total night's sleep, in 3201,
21 will support a filing of an NDA?

22 **Q.** And what was FDA's response to Vanda's question?

23 **A.** In the next two paragraphs down, the answer is: No.
24 We consider use of a biomarker instead of a clinical
25 efficacy endpoint to be a filing issue.

~~Jasket~~ - Direct

1 Q. And what is your understanding as to what FDA means
2 when they say "a filing issue"?

3 A. A filing issue is something quite serious. What it
4 means is that FDA has determined that in accord with the
5 Food, Drug, and Cosmetic Act, the substance of the
6 application is substantively incomplete and will not merit
7 a review. So they won't even pick it up; just set it
8 aside.

9 Q. Okay. And is it your understanding that this is a
10 result of Vanda persisting in its insistence on using a
11 surrogate endpoint?

12 A. Yes. The agency then continued the -- they felt that
13 you can do well-controlled clinical trials.

14 Q. And if we turn back to your timeline at DDX-2.3, into
15 2012, the next document we are going to look at is
16 JTX- 69.

17 Was Vanda persisting, at that point in time, to
18 insist on using a surrogate endpoint?

19 A. Yes. At some point, they believed that their
20 application would be appropriate for a Subpart H
21 submission, and so they made that request.

22 Q. Right. And was JTX- 69 something you considered in
23 forming your opinions?

24 A. Yes.

25 MR. LUKAS: Defendants move for JTX- 69 to be

~~Jaskot~~ - Direct

1 admitted into evidence, Your Honor.

2 **MR. STONE:** No objection, Your Honor.

3 **THE COURT:** All right. It's admitted.

4 **MR. LUKAS:** Mr. Brooks, if we could, please,
5 bring up JTX- 69.

6 (JTX-69 is admitted into evidence.)

7 **BY MR. LUKAS:**

8 **Q.** Ms. Jaskot, what is a Subpart H submission to FDA?

9 **A.** 21 CFR 314, there is a provision, Subpart H, which
10 allows for accelerated approval of an application for a
11 drug that's for a serious indication and for which there's
12 an unmet medical need. And to accelerate it, you can be
13 given approval based on a surrogate endpoint.

14 **Q.** And did Vanda request Subpart H review of its NDA for
15 tasimelteon?

16 **A.** Yes, it did.

17 **Q.** Looking at Page 1, and specifically the last sentence
18 of the paragraph at the bottom, was Vanda also requesting
19 further FDA comment on their proposed use of entrainment
20 here?

21 **A.** Yes. FDA says: You reiterate that your proposed
22 surrogate endpoint of entrainment is reasonably likely to
23 predict clinical benefit for total nighttime and daytime
24 sleep.

25 I believe it continues on the next page.

~~Jaskot~~ - Direct

1 Q. Right. If we could turn to Page 2.

2 A. We've considered your additional arguments and
3 believe that clinical efficacy can be shown via a clinical
4 benefit endpoint.

5 Q. So did FDA refuse to have any further discussion of
6 Subpart H at this point in time?

7 A. Vanda made quite a -- a press for the Subpart H
8 designation right into the division, of the personnel in
9 the division, the director of the Center for Drug
10 Evaluation and Research, and even to the Commissioner of
11 FDA.

12 In my 30 years, I've never written to the
13 Commissioner of FDA.

14 So they were very strongly in favor of gaining the
15 Subpart H designation. And FDA said, no, we will not,
16 again, meet with you on Subpart H as it would not be
17 productive. But they did agree to meet with them if they
18 wanted to discuss a clinical endpoint that was an actual
19 benefit.

20 Q. Right. What was the clinical endpoint that would
21 have been of actual benefit, according to FDA?

22 A. That's the 25 percent of total nights sleep, worst
23 nights; 25 percent of worst days versus naps.

24 Q. Okay. If we could turn back to your timeline,
25 Ms. Jaskot, PDX- 2.3.

~~Jaskot~~ - Direct

1 There was a subsequent communication in November of
2 2012; is that right?

3 **A.** Correct.

4 **Q.** And just to briefly touch on this JTX- 67, did you
5 review that document in forming your opinions?

6 **A.** Yes, I did.

7 **MR. LUKAS:** Defendants move to have JTX- 67
8 admitted into evidence, Your Honor.

9 **MR. STONE:** No objection, Your Honor.

10 **THE COURT:** It's admitted.

11 (JTX-67 is admitted into evidence.)

12 **BY MR. LUKAS:**

13 **Q.** If we can bring up JTX- 67, what is the general
14 content and format of this document, Ms. Jaskot?

15 **A.** This is the response that FDA provided with regard to
16 the statistical analysis plan submitted by Vanda. And
17 it's not typically in the Q&A format, but it's -- I guess
18 there was just one question and one answer.

19 **Q.** Okay. So at this point in time, had Vanda completed
20 its clinical studies for tasimelteon?

21 **A.** Yes.

22 **Q.** And they're proposing to analyze those studies using
23 their endpoints; is that right?

24 **A.** That's correct.

25 **Q.** And what were the endpoints that Vanda was proposing

1 to use as a primary efficacy for its Phase 3 III clinical
2 studies at this point?

3 **A.** They were, again, requesting -- or they, again, asked
4 for the Subpart H designation. And in this letter, FDA
5 is, again, refusing it. And they're saying they want at
6 least one clinical trial demonstrating efficacy on an
7 appropriate clinical outcome, and that would be necessary
8 for approval.

9 **Q.** Right. And if we turn to Paragraph 3, specifically
10 the bottom.

11 How did FDA respond to Vanda in November of 2012?

12 **A.** They, again, said that they would -- it would be a
13 filing issue if they did not include clinical efficacy
14 endpoints. And they said if you don't submit these, then
15 we will select for use in filing decisions, a clinical
16 endpoint they deemed to fulfill the minimum requirements.

17 **Q.** Okay. Turning back to -- well, first of all, did
18 Vanda take FDA's advice in this case?

19 **A.** No, they did not.

20 **Q.** And turning back to DDX-2.3, the timeline.

21 Vanda nonetheless submitted its NDA later in 2013; is
22 that right?

23 **A.** Yes. They submitted in May of 2013. Received
24 approval eight months later in January 2014.

25 **Q.** Okay. And were you here yesterday when

~~Jaskot~~ - Direct

1 Dr. Polymeropoulos discussed JTX- 110?

2 **A.** Yes.

3 **Q.** And is there a discussion in that document of the
4 FDA's review of surrogate endpoints that were proposed by
5 Vanda?

6 **A.** Yes, there were.

7 **MR. LUKAS:** If we could, please, bring up
8 JTX- 110 at Page 39.

9 **BY MR. LUKAS:**

10 **Q.** And the second paragraph there, is this the portion
11 of that document relating to the surrogate endpoints?

12 **A.** Yes. And they discuss that approval of a drug under
13 505(b) (1). It's based on efficacy data appropriate
14 clinical endpoints or on validated surrogate marker. And
15 they say that the melatonin metabolite is not a validated
16 surrogate marker.

17 **MR. STONE:** Your Honor, forgive me. The copy
18 of the exhibit in the binder that I received from
19 defendants appears to have highlighting on it. I just
20 want to note for the record that that's not in the
21 original. I suspect that this is an accident.

22 **MR. LUKAS:** It was a mistake, yes.

23 **MR. STONE:** I'm sure you'll want to supplement,
24 and I have no objection to their doing so.

25 **THE COURT:** Okay. Thank you.

~~Jaskot - Direct~~

1 **MR. STONE:** Because I figured the Court's copy
2 had it, too, I wanted to point out that that's not
3 actually in the original FDA document.

4 **MR. LUKAS:** That's correct. Thank you,
5 Counsel.

6 **THE COURT:** Thank you.

7 **BY MR. LUKAS:**

8 **Q.** What is your understanding of the -- is there an FDA
9 regulation that goes to surrogate endpoints?

10 **A.** Yes, there is. I don't have it cited in front of me.

11 **Q.** Well, did you prepare a demonstrative on that FDA
12 regulation?

13 **A.** Yes.

14 **MR. LUKAS:** If we could bring up DDX- 2.4.

15 **BY MR. LUKAS:**

16 **Q.** How, if at all, does this regulation inform your
17 analysis in this case?

18 **A.** This regulation requires that if your approval is
19 based on a surrogate clinical endpoint, that there must be
20 a statement in the labeling saying such that it included a
21 succinct description of the limitations of usefulness of
22 the drug and any uncertainty about anticipated clinical
23 benefits.

24 So it's flagged in the labeling if a surrogate was
25 relying on that.

~~Jaskot~~ - Direct

1 Q. Okay. And no such flag is apparent in the Hetlioz
2 label; is that fair?

3 A. No.

4 Q. Okay. Turning back to DDX- 2.3, your timeline, there
5 is a JTX-84 that you cite in January 23, 2014.

6 Generally speaking, what is JTX- 84?

7 A. This is a summary review that FDA prepares shortly
8 after they've approved a drug. And it just memorializes a
9 multidisciplinary review that the drug received.

10 Q. Okay.

11 MR. LUKAS: Defendants move to have JTX- 84
12 admitted into evidence, Your Honor.

13 MR. STONE: No objection, Your Honor.

14 THE COURT: All right. It's admitted.

15 MR. LUKAS: Thank you.

16 (JTX-84 is admitted into evidence.)

17 BY MR. LUKAS:

18 Q. And is this a document that's prepared by FDA?

19 A. Yes, it is.

20 Q. And is it prepared after there was an advisory
21 committee meeting?

22 A. Yes.

23 Q. And does this document include the FDA's basis for
24 recommending approval of a drug product?

25 A. Yes, it does.

~~Jaskot~~ - Direct

1 Q. And in this case, that would be Hetlioz?

2 A. Correct.

3 Q. And if we could go to Page 9, Section 13 of this
4 document.

5 What are we seeing here, Ms. Jaskot?

6 A. This is the decision and recommendation of approval
7 of tasimelteon.

8 Q. Does the reviewer in this case provide any commentary
9 on why the tasimelteon drug product is being approved?

10 A. Yes. They cite that even though agreement was never
11 reached with the applicant regarding the primary endpoints
12 to be used in the pivotal studies, the applicant opted to
13 use biomarkers-based endpoints that the division did not
14 agree with. But they had also, as a secondary endpoint,
15 submitted upper quartile and daytime -- lower quartile of
16 nighttime sleep and upper quartile of daytime sleep.

17 Q. So would it be fair to say that the FDA did not
18 consider the biomarker -- biomarker-based endpoints in
19 reviewing the tasimelteon NDA?

20 A. Yes. In my experience, they did something unusual.
21 They took the secondary endpoint, which is, as we
22 discussed, prior to secondary endpoints that are
23 sufficient to warrant approval, they took the secondary
24 endpoint and redesignated it as the primary endpoint and
25 granted the approval only on the clinical endpoints.

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1 Q. And is the use of these other secondary endpoints
2 that approval was based on, is that reflected in the
3 FDA-approved label for Hetlioz?

4 A. Yes.

5 Q. Ms. Jaskot, I believe there's a document JTX- 28 in
6 your binder.

7 A. Yes.

8 Q. Do you recognize that document?

9 A. Yes.

10 Q. What is it?

11 A. This is the approved Hetlioz label.

12 MR. LUKAS: If we could, please, bring that up,
13 Mr. Brooks.

14 BY MR. LUKAS:

15 Q. Now, what is the indication for which Hetlioz is
16 approved?

17 A. For the treatment of Non-24 Sleep-Wake Disorder in
18 adults.

19 Q. And does this indication and usage section -- I think
20 we've heard testimony about this.

21 Does this include the words "entrain" or
22 "entrainment"?

23 A. No, it does not.

24 Q. Now, Ms. Jaskot, you testified earlier, part of your
25 responsibilities at Teva and at other companies was to

~~Jaskot~~ - Direct

1 prepare and review FDA-approved labeling; is that right?

2 **A.** That's correct.

3 **Q.** Now, in your experience, when does the preparation of
4 a proposed label for submission to FDA typically begin?

5 **A.** Typically, it's after the data from the clinical
6 trials are available and the -- that data, combined with a
7 lot of other data information that's been developed on the
8 drug, is combined into a draft label.

9 **Q.** Okay. And is that draft label submitted to FDA,
10 typically?

11 **A.** Yes.

12 **Q.** Did you review a draft label in forming your opinions
13 in this case?

14 **A.** Yes, I did.

15 **Q.** And turning to DTX- 139 in your binder, is this a
16 draft label?

17 **A.** That's still the approved label. Okay. Yes. It's
18 in 139.

19 **MR. STONE:** Could you hold on for a second? I
20 have to find it in my binder. I just found it. I
21 apologize.

22 **MR. LUKAS:** Okay. If we could, please, bring
23 up DTX- 139. It's already been admitted into evidence.

24 **BY MR. LUKAS:**

25 **Q.** Ms. Jaskot, did this draft label for tasimelteon in

~~Jaskot~~ - Direct

1 the Indications and Usage and Dosage -- Dosage and
2 Administration sections include a discussion of
3 entrainment?

4 **A.** Yes, it did. It's both in the Indications and Usage,
5 as well as extensive discussion in the Dosage section.

6 **Q.** And did you prepare -- turning to Section 14 of this
7 document, is there also a discussion of entrainment in
8 this section?

9 **A.** Yes, there's some extensive discussion of entrainment
10 and circadian regulation.

11 **Q.** Right. What is Section 14 of the label typically --
12 or what does FDA require that Section 14 of a label
13 include?

14 **A.** The clinical study section is limited to that
15 clinical data that was used to support the approved
16 indication.

17 **Q.** Okay. Did you prepare a demonstrative summarizing or
18 highlighting some of the language in DTX- 139?

19 **A.** Yes, I did.

20 **MR. LUKAS:** If we could go to DDX- 2.5.

21 **BY MR. LUKAS:**

22 **Q.** What are we looking at here, Ms. Jaskot?

23 **A.** This is a side by side. What's on the right is the
24 approved Hetlioz label. What's on the left, highlighted,
25 is language dealing with entrainment, the metabolite,

~~Jaskot~~ - Direct

1 synchronization, et cetera. And all that highlighted
2 language was removed by FDA from the labeling prior to
3 approval.

4 **Q.** And does FDA have regulations concerning what must be
5 included and can be included in this section of labels?

6 **A.** Yes.

7 **MR. LUKAS:** If we could bring up DDX- 2.6.

8 **BY MR. LUKAS:**

9 **Q.** What are we looking at here, Ms. Jaskot?

10 **A.** These are kind of reciprocating regulations, dealing
11 with the Indication section first and then the Clinical
12 Study section.

13 The regulation on the Indication section says that
14 only the indication that is supported by substantial
15 evidence of effectiveness can be included in that section.

16 Conversely, the Clinical Study section cannot imply
17 any other use, other than what's in the Indication
18 section.

19 **Q.** So in your opinion, the fact that the entrainment was
20 taken out of the Clinical Study section, is that reflected
21 at all in other parts of the label for Hetlioz?

22 **A.** I don't understand the question.

23 **Q.** Sorry.

24 **MR. LUKAS:** If we could go back to DDX- 2.5.

25

~~Jaskot - Direct~~

1 **BY MR. LUKAS:**

2 **Q.** So -- so under the FDA regulations that you just
3 discussed, what effect, if any, did those regulations have
4 on the other parts of the label due to the fact that
5 entrainment was taken out or removed and is not present in
6 Section 14 of the label here?

7 **A.** Well, as I said, they are reciprocating. If, indeed,
8 the Clinical Study section implied an indication of
9 entrainment, it would not have been approved. It would be
10 outside of allowable regulation. And, of course, as we've
11 seen, the indication is not listed in the Indication
12 section.

13 **Q.** And it's fair to say that the FDA-approved -- is it
14 fair to say that the FDA-approved label for Hetlioz in the
15 Clinical Studies section doesn't include the words
16 "entrain" or "entrainment"?

17 **A.** That's correct.

18 **Q.** And why is that?

19 **A.** FDA considered the surrogates and decided early on
20 that they were not appropriate for approval of the drug
21 product. And the entrainment is essentially the
22 surrogate. So they didn't just take out the mention of
23 the metabolite, they took out entrainment by design from
24 the label.

25 **Q.** Now, how, if at all, does this impact Vanda's ability

~~Jaskot~~ - Direct

1 to market its drug product?

2 **A.** Well, it cannot market for anything outside the four
3 corners of the label. So it could not market for
4 entrainment or synchronization.

5 **Q.** Okay. Ms. Jaskot, have you reviewed Apotex's and
6 Teva's proposed labeling for their generic products?

7 **A.** Yes, I have.

8 **Q.** And those are JTX- 30 and JTX- 33 in your binder?

9 **A.** Yes.

10 **Q.** Do FDA regulations also govern what Teva and Apotex
11 must include in their FDA labels?

12 **A.** Yes. The generic labels must be essentially the same
13 as the brand label.

14 **Q.** And does this mean neither of Teva's or Apotex's
15 labels include "entrain" or "entrainment"?

16 **A.** That's correct.

17 **MR. LUKAS:** I will pass the witness,
18 Your Honor.

19 **THE COURT:** All right. Cross.

20 **MR. STONE:** We have some binders to pass up as
21 well, Ms. Jaskot. I'll be with you shortly.

22 And everything that you were shown on your
23 direct examination that I plan to show you again is --
24 happens to be in the binder we're giving you now, so you
25 should need only this one.

~~Jaskot~~ - Cross

1 **THE WITNESS:** Okay.

2 **MR. STONE:** May I proceed, Your Honor?

3 **THE COURT:** Please.

4 **MR. STONE:** Thank you.

5 CROSS EXAMINATION

6 **BY MR. STONE:**

7 **Q.** Ms. Jaskot, you spent a fair amount of time on your
8 direct examination talking about the FDA's position with
9 respect to entrainment and tasimelteon, correct?

10 **A.** Yes.

11 **Q.** I believe I heard you to have said at various times
12 what FDA felt, what FDA considered, and that FDA did
13 something by design.

14 Do you recall using those words?

15 **A.** I don't know about "felt," but I possibly did.

16 **Q.** Okay. I wrote it down. I could have misheard you.

17 In forming your opinions in this case, you didn't
18 speak to anyone at FDA, correct?

19 **A.** Not on this topic, no.

20 **Q.** And you've never worked at FDA yourself, correct?

21 **A.** That's correct.

22 **Q.** And so to the extent that you were telling -- well,
23 withdrawn.

24 You weren't at the advisory committee meeting for
25 tasimelteon, correct?

1 **A.** No, but I have been at advisory committee meetings
2 with that division of...

3 **Q.** We're going to come to that, I promise. But for
4 purposes of this, let's just stay with my question.

5 You weren't at the advisory committee for
6 tasimelteon, correct?

7 **A.** That's correct.

8 **Q.** Okay. And so to the extent that you are telling the
9 Court here what FDA felt, what FDA considered, what FDA
10 did by design, the total of that comes from reading the
11 documents in this case; you have no personal knowledge,
12 you weren't there, you haven't spoken to anyone directly,
13 correct?

14 **A.** I was not there, that's correct.

15 **Q.** Okay. I want to talk about the label for Hetlioz,
16 and I want to see if we can zoom out a little bit.

17 The label is sometimes called "the package insert" or
18 the "prescribing information," correct?

19 **A.** Yes.

20 **Q.** You've heard both of those terms?

21 **A.** I have.

22 **Q.** Now, the version that you just showed the Court on
23 your direct examination that has information about the
24 urinary metabolite, you did a demonstrative on it, that
25 version came from Vanda's files in this litigation,

~~Jaskol~~ - Cross

1 correct?

2 **A.** I believe so, yes.

3 **Q.** It has a Vanda Bates stamp on it, correct?

4 **A.** Yes. Yes.

5 **Q.** You were asked whether draft labels are submitted to
6 FDA, and your answer was "typically, yes."

7 Do you recall that?

8 **A.** They are an integral part of an NDA.

9 **Q.** And let's talk about that.

10 You worked in a part of Teva for many years in which
11 labels were created, correct?

12 **A.** That's correct.

13 **Q.** And if -- Teva is both a generic and a branded drug
14 company depending on which drug, correct?

15 **A.** That's correct.

16 **Q.** And you had experience with both?

17 **A.** Yes. At one point, they were combined under my
18 leadership.

19 **Q.** Where Teva is acting is a branded pharmaceutical
20 company, and in your expectation any branded
21 pharmaceutical company, internally there are drafts of the
22 draft label before it actually goes to FDA, correct?

23 **A.** Yes.

24 **Q.** Someone junior writes a version, someone senior says,
25 I don't like that part, it gets changed, it gets

1 discussed, eventually it gets handed over, correct?

2 **A.** Undoubtedly there are multiple versions of it.

3 **Q.** Right. And you have no personal knowledge, one way
4 or the other, whether the version you've been talking
5 about was actually given to FDA, correct?

6 **A.** It was presented to me as such, that it was a draft.

7 **Q.** It was presented to you as such by counsel for the
8 defendants, correct?

9 **A.** Yes.

10 **Q.** Right. And just to be clear, you can't tell this
11 Court that that is a version that FDA ever saw, correct?

12 **A.** I think its pretty clear that whatever was submitted
13 was in line with Vanda's proposed studies, which would
14 have included the surrogates.

15 **Q.** Well, let's start with my question.

16 The version that you've testified about today, you
17 have no idea if FDA ever actually saw that version,
18 correct?

19 **A.** No. That's correct.

20 **Q.** Now, one of the questions that the Court is going to
21 have to answer in this case is whether the actually
22 approved label instructs, recommends, promotes, encourages
23 or suggests that a doctor practice the steps of the claim.

24 Generally, your familiar with that concept, correct?

25 **A.** Yes.

Jaskot - Cross

1 Q. A doctor who is prescribing tasimelteon, is not going
2 to have access to draft FDA labels, correct?

3 A. That's correct.

4 Q. They're not going to subpoena Vanda and ask for
5 drafts in their files, correct?

6 A. That's correct.

7 Q. They're going to look at the final label as it exits,
8 correct?

9 A. Correct.

10 Q. They're not going to know what wasn't in there and
11 was on a draft, correct?

12 A. That also is correct.

13 Q. Now, were you here in court when Dr. Combs, Vanda's
14 expert, showed the Court that in his expert opinion as a
15 treating sleep physician, the label recommends that it be
16 administered one hour before bedtime at the same time
17 every night?

18 Were you here when he talked about that?

19 A. Yes.

20 Q. Do you know why the label says: Taken at the same
21 time every night?

22 A. From a regulatory perspective, which is my only
23 perspective on this, it's in line with how the dosing was
24 done in the clinical trials.

25 Q. Okay. But from your perspective, whether that is or

~~Jasko~~ - Cross

1 isn't to a sleep physician evidence that it works by
2 entrainment, you have no view on that subject, correct?

3 **A.** You would have to ask a physician. I don't have a
4 view.

5 **Q.** Okay. I'd like you to turn in the binder to PTX- 5.
6 The way we've organized your binder is that the joint
7 exhibits, the Js come first, then the plaintiffs the Ps.
8 So PTX- 5.

9 Are you there?

10 **A.** Yes.

11 **Q.** Thank you, ma'am.

12 You recognize this to be a -- an article that
13 appeared in the journal Drugs, and is entitled "Diagnosis
14 and Treatment of Non-24-hour Sleep-Wake Disorder in the
15 Blind"?

16 **A.** Yes.

17 **MR. STONE:** Your Honor, I'd offer PTX-5.

18 **MR. LUKAS:** No objection, Your Honor.

19 **THE COURT:** All right. It's admitted.

20 (PTX-5 admitted into evidence.)

21 **MR. STONE:** Mr. Weir, would you please put up
22 the first page and give us the title and the authors.

23 No, I have to switch it over. I apologize.

24 Mr. Weir can do many things, but he can't reach
25 this button from that far away. Apologies.

Jaskot - Cross

1 Mr. Weir, would you please now bring up the
2 title and the authors.

3 **BY MR. STONE:**

4 **Q.** The authors of this article, Ms. Jaskot, are Jonathan
5 Emens and Charmane Eastman, correct?

6 **A.** Yes.

7 **Q.** Both of those names are familiar to you?

8 **A.** I saw the names for the first time during our
9 deposition in November.

10 **Q.** Okay. Well, Jonathan Emens is one of the experts for
11 the defendants. I haven't looked behind me, but I think
12 he's sitting in the courtroom.

13 He's been here, correct?

14 **A.** I don't know. I wouldn't recognize him.

15 **Q.** Okay. And Charmane Eastman you saw in your review
16 because she was actually at the advisory committee
17 meeting, right?

18 **A.** Yes.

19 **MR. STONE:** Why don't we, Mr. Weir, come to the
20 first full paragraph on the left what's called the
21 "abstract."

22 **BY MR. STONE:**

23 **Q.** I want to direct you, Ms. Jaskot, halfway down this
24 paragraph, there is a sentence that begins with the word
25 "orally."

~~Jaskot~~ - Cross

1 Do you see that there?

2 **A.** Yes.

3 **Q.** And what this article written by one of the
4 defendants' experts and one of the people at the advisory
5 committee says is: Orally administered melatonin and the
6 melatonin agonist tasimelteon have been shown to entrain
7 (synchronize) the circadian clock resulting in
8 improvements in night-time sleep and daytime alertness.

9 Do you see that there?

10 **A.** Yes.

11 **Q.** In all of the reviews of the document you have seen,
12 have you ever seen a document in which FDA says that's not
13 how the drug works?

14 **A.** Not in those specific terms. But I also -- as I
15 testified, FDA removed that language from the labeling.

16 **Q.** Well, let's be clear about what happened there, and
17 we're going to come to it, I promise.

18 FDA never removed anything that says tasimelteon has
19 been shown to entrain the circadian clock. What FDA
20 removed is the word "entrainment" and the urinary
21 metabolite data, correct?

22 **A.** I'll have to take your word for it unless you want me
23 to compare the labeling.

24 **Q.** It is a little difficult to ask you to confirm that
25 something never happened in thousands of pages of

~~Jaskot~~ - Cross

1 documents, so why don't we move on. But that's fine,
2 thank you.

3 You talked on your direct examination about surrogate
4 endpoint resources for -- well, withdrawn. I'm ahead of
5 myself.

6 You talked about surrogate endpoints, correct?

7 **A.** Yes.

8 **Q.** And you talked about biomarkers.

9 **A.** Yes.

10 **Q.** Okay. A good example of a biomarker is blood
11 pressure, correct?

12 **A.** Yes.

13 **Q.** One might choose to measure blood pressure in a study
14 rather than, God forbid, waiting to see if people have
15 heart attacks, correct?

16 **A.** Yes.

17 **Q.** Cholesterol is a good biomarker. One can look to see
18 whether cholesterol is elevated and make decisions about
19 that without, again, waiting for the clinical consequences
20 which might be dire, correct?

21 **A.** Correct.

22 **Q.** I'd like you to turn in your binder to JTX-164.

23 Do you recognize this to be a printout from FDA's
24 website called Surrogate Endpoint Resources for Drug
25 Biologic Development?

~~Jaskot~~ - Cross

1 **A.** Yes.

2 **MR. STONE:** Your Honor, I offer JTX-164.

3 **MR. LUKAS:** No objection.

4 **THE COURT:** It's admitted.

5 (JTX-164 admitted into evidence.)

6 **BY MR. STONE:**

7 **Q.** Now, you actually covered a lot of this on your
8 direct. And I don't want to repeat, but just so that we
9 can set up as we go through this, a clinical measurement
10 is something about whether a patient is functioning
11 better, feels better, or survives longer, correct?

12 **A.** Correct.

13 **Q.** A surrogate endpoint is something other than that,
14 correct?

15 **A.** It stands in its place, yes.

16 **Q.** Right. And one kind of surrogate endpoint can be a
17 biomarker, correct?

18 **A.** Yes.

19 **Q.** And if we were testing atorvastatin, my personal
20 favorite, Lipitor, we might look to see whether it lowers
21 cholesterol rather than waiting to see if it prevents
22 heart attacks, correct?

23 **A.** Yes.

24 **Q.** Okay. And so what's going on over the life of the
25 approval process of tasimelteon that you showed us is that

~~Jaskot~~ - Cross

1 Vanda is telling FDA that the urinary metabolite of
2 melatonin that is called aMT6s at -- measured at various
3 times of the day is a surrogate, a biomarker, for whether
4 the person's circadian rhythm is entrained to the normal
5 light/dark cycle, correct?

6 That's Vanda position.

7 **A.** Yes.

8 **Q.** And FDA is saying, in response, we don't have any
9 evidence sufficient to validate that biomarker other than
10 the study that you are currently doing, correct?

11 **A.** Correct.

12 **Q.** And what FDA is saying, repeatedly, is, we require
13 prior evidence that a biomarker works. Essentially, you
14 can't come to us with a study that says, look, I proved
15 this biomarker works, approve the drug.

16 The biomarker has to get approved in advance,
17 correct?

18 **A.** Correct.

19 **Q.** And Vanda is saying that for a disease or a
20 condition, the sine qua non of which is a lack of
21 entrainment, clinical benefit is secondary; what you want
22 to measure is the biomarker.

23 That's Vanda's position, correct?

24 **A.** Yes.

25 **Q.** And you told us on your direct examination that

1 ordinarily the sponsor and FDA agree in advance on what
2 the endpoint is going to be. Doesn't always happen, but
3 it often does, correct?

4 **A.** Correct.

5 **Q.** And it didn't here. We can agree, correct?

6 **A.** Correct.

7 **Q.** To the very end, Vanda's contention was that the best
8 way to look for entrainment was to measure the urinary
9 metabolite, aMT6s, and to the very end, FDA was saying, we
10 will not accept that as a primary endpoint; we want to see
11 clinical benefit in patients. Correct?

12 **A.** Correct.

13 **Q.** And when it gets to the advisory committee, the first
14 thing FDA says to everyone who comes is we actually have a
15 dispute about what the endpoints are, correct?

16 **A.** Correct.

17 **Q.** But we are, nevertheless, recommending approval of
18 the drug, correct?

19 **A.** Based on the secondary endpoint, yes.

20 **Q.** Okay. Let's see if we can agree on something that we
21 disagree about, which is do we disagree about this.

22 That was a terrible question. I will withdraw it.

23 I would like to see if we agree on this. It is
24 Vanda's contention that while FDA refused to accept the
25 aMT6s measurement as a biomarker for entrainment, the

~~Jaskot~~ - Cross

1 clinical data on which FDA was relying were clinical
2 benefits from entrainment.

3 That's Vanda's position. Do you agree with them?

4 **A.** No, I don't.

5 **Q.** Okay. Now, one of the documents that you looked at
6 on your direct examination was JTX-110, the materials that
7 went to the attendees at the advisory committee meeting.

8 Can we look at that again, please?

9 **A.** Yes.

10 **Q.** You told us on your direct -- or actually, I think,
11 on my cross, that you've been to advisory committee
12 meetings, correct?

13 **A.** Yes.

14 **Q.** FDA often convenes meetings of -- advisory committee
15 meetings to get input when they are considering approving
16 a drug, correct?

17 **A.** That's true.

18 **Q.** The invitees include patients, patient advocacy
19 groups, specialists or experts in the field?

20 **A.** Yes.

21 **Q.** Okay. And if we look at the title of this, this one
22 was held in a ballroom at a hotel in Maryland, correct?

23 **A.** Yes.

24 **Q.** On November 14, 2013, correct?

25 **A.** Yes.

~~Jascot~~ - Cross

1 Q. It lasted all day?

2 A. Uh-huh.

3 Q. And if we turn to the next page, other than a table
4 of contents, what we see on Page 3 --

5 MR. STONE: And Mr. Weir, would you bring up
6 JTX-110 at Page 3.

7 BY MR. STONE:

8 Q. -- we see a memo from Ronald Farkas, MD, the clinical
9 team leader for the Division of Neurology Products, to
10 everybody who is coming, members and invited guests,
11 laying out the briefing memo that's about to follow,
12 correct?

13 A. Yes.

14 Q. This is the cover memo, correct?

15 A. Yes.

16 Q. And if we turn to the next page, Page 4 --

17 MR. STONE: Mr. Weir, would you bring up the
18 second paragraph.

19 BY MR. STONE:

20 Q. -- Dr. Farkas writes to the invited guests: You will
21 see in the reviews by Drs. Jillapalli and Luan -- for the
22 court reporter's benefit, that's J-I-L-L-A-P-A-L-L-I and
23 Luan is L-U-A-N. Let's pause there.

24 Ms. Jascot, Dr. Jillapalli was the primary reviewer
25 of the application for FDA, correct?

~~Jaskot~~ - Cross

1 **A.** For the clinical study, yes.

2 **Q.** For the clinical study.

3 And Dr. Luan was the statistical analyst, correct?

4 **A.** Yes.

5 **Q.** Dr. Farkas writes: You will see in the reviews by
6 Drs. Jillapalli and Luan that during the development of
7 the tasimelteon agreement was not reached between the
8 sponsor and the Division on a primary efficacy endpoint
9 for either study 3201 or 3203.

10 Do you see that there?

11 **A.** Yes.

12 **Q.** "Division" is FDA, correct?

13 **A.** Yes.

14 **Q.** And 3201 and 3203 are what we now call SET and reSET?

15 **A.** Yes.

16 **Q.** And then it says: The Sponsor proposed a primary
17 endpoint of entrainment of the circadian melatonin rhythm
18 as measured by the urinary metabolite of melatonin, aMT6s.

19 Do you see that there?

20 **A.** Yes, I do.

21 **Q.** And you agree that's what Vanda proposed?

22 **A.** Yes.

23 **Q.** And then Dr. Farkas continues: The division did not
24 accept a biomarker-based endpoint because a wealth of
25 existing scientific knowledge about circadian rhythms

1 suggested that the clinical benefit from entrainment in
2 Non-24 would occur in a reasonably brief period of time,
3 and would be readily measurable in terms of benefit on
4 sleep.

5 Do you see that there?

6 **A.** Yes.

7 **Q.** Now, this is the first substantive paper of what
8 everyone coming to the advisory committee is going to read
9 when they read the book, correct?

10 **A.** Correct.

11 **Q.** And they are going to read that the difference
12 between Vanda and FDA is whether to measure entrainment by
13 a urinary metabolite or whether to measure clinical
14 benefits from entrainment.

15 That's what it says, right?

16 **A.** That's what it says, yes.

17 **Q.** Okay. Now, that's not the only time that FDA
18 described the dispute between it and Vanda as to what
19 measure -- whether to measure entrainment by a metabolite
20 or by clinical benefits, is it?

21 There's another time, correct?

22 **A.** What document are you referring?

23 **Q.** Well, but -- we'll get there in a second. Let's go
24 first.

25 You know there's another time, right?

Jaskot - Cross

1 **A.** I'll take your word for it. I don't have instant
2 recall of it.

3 **Q.** Okay. Let's look at it. That's fine.

4 Let's look at the transcript of the advisory
5 committee meeting, which is PTX-263.

6 Now, I have to introduce the exhibit, so let's lay
7 some foundation.

8 When FDA has an advisory committee meeting, they
9 record it and make a transcript, correct?

10 **A.** Yes.

11 **Q.** And this is the transcript of the meeting for
12 tasimelteon, correct?

13 **A.** Yes.

14 **Q.** And you've reviewed this before, correct?

15 **A.** Yes.

16 **Q.** You just chose not to use it as an exhibit in your
17 direct today, correct?

18 **A.** Yes.

19 **MR. STONE:** I offer PTX-263.

20 **MR. LUKAS:** No objection.

21 **THE COURT:** All right. It's admitted.

22 (PTX-263 admitted into evidence.)

23 **BY MR. STONE:**

24 **Q.** On the first page, some of the participants
25 introduced themselves, correct?

~~Jaskot~~ - Cross

1 **A.** Yes.

2 **Q.** They go around the table and say hi, correct?

3 **A.** Yes.

4 **Q.** And one of the names we see there is Charmane
5 Eastman. She's the coauthor with Dr. Emens of the article
6 that says tasimelteon works by entrainment, correct?

7 **A.** She's the coauthor, yes.

8 **MR. STONE:** And then let's go to the top of the
9 next page. Mr. Weir, if you pull up Page 2, please.

10 And pull up the top half before the text
11 gets -- that's great. Thank you.

12 **BY MR. STONE:**

13 **Q.** Four names down, we see Dr. Luan and Dr. Jillapalli,
14 correct?

15 **A.** Correct, yes.

16 **Q.** Under them, we see Dr. Farkas who wrote the
17 introductory memo, correct?

18 **A.** Yes.

19 **Q.** And then we see Eric Bastings, the acting director of
20 the Division of Neurology Products, correct?

21 **A.** Yes.

22 **Q.** He gave the introductory remarks for the day?

23 **A.** Yes.

24 **Q.** All right. And those introductory remarks start on
25 Page 3, at the very bottom?

~~Jaskot~~ - Cross

1 **A.** Yes.

2 **Q.** He says: Good morning, and I want to welcome people
3 back.

4 Do you see that there?

5 **A.** Yes, I do.

6 **MR. STONE:** Let's turn to the top of Page 4.

7 And Mr. Weir, if you would blow up the first three
8 paragraphs.

9 **BY MR. STONE:**

10 **Q.** This is -- to be clear and for the benefit of the
11 Court, this is the transcript of what Dr. Bastings said
12 that day, correct?

13 **A.** Yes.

14 **Q.** FDA usually cleans it up. They take out the "uhmms,"
15 but it's usually pretty good, right?

16 **A.** Yes.

17 **Q.** He says, in what's recorded as the first paragraph
18 here, that Vanda had submitted the results of two studies,
19 what we now know as SET and RESET, as will be discussed by
20 Dr. Jillapalli, the medical reviewer, and Dr. Luan, the
21 statistical reviewer.

22 Do you see that there?

23 **THE COURT:** Stop. Stop for a second.

24 **MR. STONE:** Apologies, Your Honor.

25 **THE COURT:** Okay. Sorry. I was on the wrong

~~Jaskot~~ - Cross

1 page. I couldn't find it.

2 Sorry. Go ahead and pick up. Sorry.

3 **MR. STONE:** Thank you, Your Honor.

4 **BY MR. STONE:**

5 **Q.** Directing your attention, Ms. Jaskot, and for the
6 record, to Page 4 of PTX-263.

7 You're there?

8 **A.** Yes.

9 **Q.** Great.

10 Dr. Bastings, speaking to the assembled guests, then
11 says: An agreement on the primary endpoint could not be
12 reached with the Sponsor during the development program.

13 Do you see that?

14 **A.** Yes.

15 **Q.** The Sponsor proposed a primary endpoint of
16 entrainment of the circadian melatonin rhythm as measured
17 by urinary metabolite of melatonin, aMT6s.

18 Do you see that?

19 **A.** Yes.

20 **Q.** And you agree that that was Vanda's position?

21 **A.** Yes.

22 **Q.** And Dr. Bastings explains that, quote: FDA did not
23 accept a biomarker-based primary endpoint because FDA felt
24 that the clinical benefit from entrainment in Non-24 would
25 occur in a reasonably brief period of time and would be

1 readily measurable. In that setting, FDA asked the
2 Sponsor to propose a primary endpoint capable of
3 demonstrating a clinical benefit, but the Sponsor decided
4 to maintain the biomarker-based primary endpoint.

5 Do you see that there?

6 **A.** Yes.

7 **Q.** So now we have seen that FDA has told everyone who
8 comes to the advisory committee, both in the cover memo
9 and in the first things that get said to them in the
10 introductory remark, that the debate between Vanda and FDA
11 is, do we measure entrainment with a biomarker, or do we
12 measure entrainment with clinical benefit. Correct?

13 **A.** I don't necessarily see that in that last paragraph.

14 **Q.** The FDA felt the clinical benefit from entrainment
15 would be readily measurable. That's what it says,
16 correct?

17 **A.** Yes. And the following sentence says they asked the
18 sponsor to propose a primary endpoint capable of
19 demonstrating a clinical benefit. That does not say
20 entrainment.

21 **Q.** So it's your suggestion that the reason the Court
22 should find that the clinical benefit being discussed in
23 this case has nothing to do with entrainment is because he
24 didn't repeat those words in the second sentence of that
25 paragraph?

~~Jaskot~~ - Cross

1 **A.** No, it's not just that.

2 **Q.** Another person at this meeting -- well, let me ask
3 you this. When he said "the clinical benefit from
4 entrainment" and when his colleague wrote it down, do you
5 think that's a typo?

6 **A.** No, I think it appears in a lot of the documents. It
7 appears that FDA used it. Vanda certainly used it.

8 **Q.** Okay.

9 **A.** When it came to memorializing the approval of the
10 drug in the insert labeling, they did not use it. In
11 fact, they took it out.

12 **Q.** Well, let's get there in pieces.

13 I think one thing we can all agree on, I think the
14 people in the hallway can agree at this point, the label
15 doesn't have the word "entrainment" in it, correct?

16 **A.** That's correct.

17 **Q.** And you have certainly shown us a draft label from
18 Vanda's files that did have the word "entrainment" in it,
19 correct?

20 **A.** Yes.

21 **Q.** While talking about the urinary metabolite, correct?

22 **A.** Yes.

23 **Q.** Now, another person who was at this meeting is Nathan
24 Fountain.

25 Do you remember that name?

~~Jaskot~~ - Cross

1 **A.** Yes.

2 **Q.** He's the chair of the advisory committee, correct?

3 **A.** Yes.

4 **MR. STONE:** Let's look at Page 33 of this
5 exhibit, Mr. Weir.

6 And Mr. Weir, if you'd bring up about five
7 sections -- yeah, you've got it.

8 **BY MR. STONE:**

9 **Q.** Dr. Fountain says: Thank you. I have a question,
10 and that is I think the data you've shown and the
11 discussion of Dr. Czeisler shows that you're entraining
12 the rhythm, and simple hypnotics or sedatives don't fix
13 things.

14 Do you see that there?

15 **A.** Yes.

16 **Q.** So the chair of the committee, the advisory
17 committee, thinks that the data is showing entraining of
18 the rhythm, correct?

19 **A.** That's what he says, yes.

20 **Q.** All right. Now, one of the things that FDA did in
21 approving tasimelteon was insisting that Vanda correlate
22 the sleep data, upper quartile of daytime naps and lower
23 quartile of nighttime sleep, with the entrainment data,
24 the metabolite, correct?

25 **A.** I don't recall that request from FDA.

~~Jaskot~~ - Cross

1 Q. That's fair.

2 If you would turn to your binder to PTX-233.

3 You understand from your vast personal experience
4 that when there's advisory committee, the sponsor also
5 provides a briefing memo, correct?

6 A. Correct.

7 Q. Do you recognize PTX-233 to be Vanda's briefing memo
8 for the advisory committee?

9 A. Yes.

10 MR. STONE: I offer PTX-233.

11 MR. LUKAS: No objection.

12 MR. STONE: Mr. Weir, would you turn in this
13 document to Page 95. And just so we can --

14 THE COURT: So it's clear, it is admitted.

15 (PTX-233 admitted into evidence.)

16 MR. STONE: I apologize, Your Honor.

17 THE COURT: Go ahead.

18 BY MR. STONE:

19 Q. And just to set the stage for the Court, this is a
20 117-page memo that all the members of the advisory
21 committee would have had in advance, correct?

22 A. Yes.

23 Q. And if we turn to Page 95 of it, we see two tables.

24 MR. STONE: Can you blow up the tables?
25

Jaskot - Cross

BY MR. STONE:

Q. What this is comparing is the difference in nighttime sleep and the difference in daytime sleep as correlated with the urinary metabolite data.

Is this something you've ever reviewed before?

A. I don't recall specifically reviewing this data, no.

Q. Would it surprise you to learn that what this shows is that people getting placebo show a much bigger difference between how much they sleep when they are in phase versus how much they sleep when they are out of phase rather than people who are getting tasimelteon and who are entrained?

Would that surprise you?

A. No.

Q. Let's shift gears. I want to ask you a question about --

THE COURT: Give me a second.

MR. STONE: Of course, Your Honor.

THE COURT: Okay. Go ahead.

MR. STONE: Thank you, Your Honor.

BY MR. STONE:

Q. Let's see if we can identify, Ms. Jaskot, another thing that we might disagree about. I think it's helpful to the Court to know where we are at odds.

Over the course of FDA's review of Vanda's

~~Jaskot~~ - Cross

1 application, FDA came to equate the word "entrainment"
2 with the "biomarker," correct?

3 **A.** Yes.

4 **Q.** Okay. And so when FDA rejected, quote, entrainment,
5 what they were rejecting was the biomarker, correct?

6 **A.** No, because if FDA accepted entrainment, there would
7 have been entrainment in the labeling. And it wouldn't
8 have been entrainment based on the biomarker; it would
9 have been entrainment based on clinical benefits.

10 **Q.** Then it may be that we do disagree. Let's go through
11 this. I appreciate your candor.

12 You were shown on direct examination JTX-69. Would
13 you mind turning back to it? It's in the white binder.

14 **A.** Yes.

15 **Q.** This is a letter from -- withdrawn.

16 One of the more charming things about the agency is
17 that instead of putting dates on letters, you find the
18 date with the electronic signature on the back, correct?

19 So if we turn to JTX-69 at 3, we'll see that this
20 letter is from Russell Katz, and it's dated June 8, 2012,
21 correct?

22 **A.** Correct.

23 **Q.** And if we turn back to the first page --

24 **MR. STONE:** Mr. Weir, would you bring up the
25 last paragraph of the first page of JTX-69.

1 **BY MR. STONE:**

2 **Q.** You were actually shown this paragraph on your direct
3 examination, correct?

4 **A.** Yes.

5 **Q.** You talked to us about what subpart H is, right?

6 **A.** Correct.

7 **Q.** Let's look at the last sentence. You reiterate --
8 and this is FDA speaking to Vanda. So the "you" is Vanda,
9 correct?

10 **A.** Yes.

11 **Q.** You reiterate that your proposed surrogate endpoint
12 of, quote, entrainment is reasonably likely to predict
13 clinical benefit for total nighttime and daytime sleep.

14 Do you see that there?

15 **A.** Yes.

16 **Q.** Entrainment is in quotations mark in the document,
17 correct?

18 **A.** Yes.

19 **Q.** As it's a defined term, correct?

20 **A.** I'm not sure why they put it in quotations.

21 **Q.** Okay.

22 **A.** This isn't the only place where I've seen it equated
23 with a surrogate.

24 **Q.** Right. Let's look at the next one. Turn back to
25 JTX-67. It's the previous document in your binder.

~~Jaskot~~ - Cross

1 This is another letter from Dr. Katz. If we look at
2 the back, it's November 28th, 2012. So it's about six
3 months later.

4 **MR. STONE:** This is already in evidence.

5 Mr. Weir, would you bring up the first page of
6 JTX-67.

7 You know what, Your Honor, I apologize. I am
8 90 percent this is in evidence, but for an abundance of
9 caution, I offer JTX-67.

10 **MR. LUKAS:** No objection.

11 **THE COURT:** All right. Well, it's admitted.

12 (PTX-67 admitted into evidence.)

13 **MR. STONE:** Thank you, Your Honor.

14 And Mr. Weir, bring up the second full
15 paragraph. That one.

16 **BY MR. STONE:**

17 **Q.** We also refer to the statistical analysis plan for,
18 skipping ahead, the SET study. You specified two primary
19 objectives it says. And the first is, quote: To
20 determine the proportion of patients, quote, entrained
21 based on calculations made on urinary melatonin
22 metabolite.

23 Do you see that there?

24 **A.** Yes.

25 **Q.** "Entrained" is once again in quotation marks?

1 **A.** Yes.

2 **Q.** Let's go back to the advisory committee meeting and
3 finally let Drs. Jillapalli and Luan have their turn. So
4 that's JTX-110.

5 You told us early that Dr. Jillapalli was the medical
6 reviewer, correct?

7 **A.** Yes.

8 **Q.** One of the things that people who came to the
9 committee meeting got was a clinical review written by
10 him, correct?

11 **A.** That's correct.

12 **MR. STONE:** If you turn to JTX-110 at 7,
13 Mr. Weir.

14 **BY MR. STONE:**

15 **Q.** This is the start of his clinical review, correct?

16 **A.** Yes.

17 **Q.** And if you turn to the next page, you can see in the
18 top left his name is on it?

19 **A.** Yes.

20 **MR. STONE:** Let's jump ahead to JTX-110 at 55,
21 Mr. Weir.

22 **BY MR. STONE:**

23 **Q.** We're still in Dr. Jillapalli's clinical review. We
24 can see that from the heading, correct?

25 **A.** Yes.

~~Jaskot~~ - Cross

1 Q. Let's pull up the first paragraph.

2 As previously noted, at the time of unblinding Study
3 3201 data, the Agency did not agree with the Applicant
4 regarding the use of entrainment biomarker as a primary
5 endpoint.

6 Do you see that there?

7 A. Yes.

8 Q. And that entrainment biomarker is aMT6s, correct?

9 A. Yes.

10 Q. Let's talk about Dr. Luan, the statistician. She
11 wrote a report that they all got, too, right?

12 A. Yes.

13 Q. Let's jump ahead to Page JTX-110 at 146.

14 This is her clinical -- this is her statistical
15 review, correct?

16 A. Yes.

17 MR. STONE: And let's jump to Page 150, please,
18 Mr. Weir.

19 What I would like to do is pull up the bottom
20 of 150 and top of 151, if you could do that.

21 BY MR. STONE:

22 Q. This is the Sponsor's Efficacy Analyses section,
23 correct?

24 A. Yes.

25 Q. And describing the SET study, it says the primary

~~Jaskot~~ - Cross

1 efficacy endpoints were the following.

2 Do you see that there?

3 **A.** I do.

4 **Q.** And there are two bullets, right?

5 **A.** Yes.

6 **Q.** The first bullet says: The entrainment of the
7 circadian melatonin rhythm as measured by urinary aMT6s.

8 And then it says: Entrainment is a melatonin-based
9 biomarker.

10 Do you see that there?

11 **A.** Yes.

12 **Q.** She is literally saying to everybody who comes to the
13 advisory committee that the word "entrainment" is a
14 synonym for the biomarker, correct?

15 **A.** Yes.

16 **Q.** Now, let's look at FDA summary review, which you
17 showed us on your direct examination. That's JTX-84.

18 This is, as you said, the review in which FDA pulls
19 together why they are approving the document, the drug,
20 correct?

21 **A.** Yes, yes.

22 **Q.** And this is written by Eric Bastings, correct?

23 **A.** Correct.

24 **Q.** He is the person who gave the introductory remarks
25 that talked about the clinical benefit from entrainment,

1 correct?

2 **A.** Yes.

3 **MR. STONE:** And if we go to Page 3 of this
4 exhibit, Mr. Weir, there's a paragraph called Background.

5 Would you pull that up for us.

6 **BY MR. STONE:**

7 **Q.** Once again, there is recitation of the fact that
8 Vanda and FDA --

9 **THE COURT:** Hold on. What exhibit are we on?

10 **MR. STONE:** JTX-84.

11 **THE COURT:** Oh, 84. Sorry. Go ahead.

12 **MR. STONE:** And we are on Page 3 of it.

13 **THE COURT:** All right.

14 **MR. STONE:** Happy to wait.

15 **THE COURT:** I'm good.

16 **BY MR. STONE:**

17 **Q.** Once again, there's discussion of the fact that Vanda
18 and FDA couldn't agree on endpoints, correct?

19 **A.** Correct.

20 **Q.** And then it says, in the third sentence, which starts
21 in the fourth line, exactly there: The applicant insisted
22 on using as primary endpoint an unvalidated surrogate,
23 quote, entrainment, based on measures of the melatonin
24 biomarker.

25 Do you see that?

~~Jaskot~~ - Cross

1 **A.** Yes.

2 **Q.** Entrainment is again in quotes, correct?

3 **A.** Yes.

4 **Q.** And if you look three lines down, it is in quotation
5 marks again, correct?

6 **A.** Yes.

7 **Q.** Now, let's look at the label that you showed us on
8 your direct examination. It's DTX-139. It is in the
9 binder. It's the second-to-last document. To make it
10 easier to find, they kind of hide it in the back.

11 Let me know when you are there.

12 **A.** I'm there.

13 **MR. STONE:** Mr. Weir, can we go to Page 12 of
14 DTX-139.

15 **BY MR. STONE:**

16 **Q.** This is the section that you excerpted in your
17 demonstrative exhibit, correct?

18 **MR. STONE:** Can you pull up the table,
19 Mr. Weir?

20 **BY MR. STONE:**

21 **Q.** With apologies, ma'am, I swallowed that question.
22 Let me ask it again. Withdrawn.

23 Table 2 on Page 12 of Exhibit DTX-139 is part of what
24 you showed us in your demonstrative exhibit, correct?

25 **A.** No, I believe it was Table 3 and whatever version we

1 were looking at.

2 **Q.** Okay. Well, either way, this is a table in the draft
3 label you talked about that talks about -- and the table
4 itself talks about -- entrainment of the master body clock
5 to the 24-hour day-night cycle as measured by the
6 melatonin and cortisol rhythms.

7 Do you see that there?

8 **A.** Yes.

9 **Q.** And it's talking about both the aMT6s data and the
10 cortisol measurement, which is the different biomarker,
11 correct?

12 **A.** Correct.

13 **Q.** What Vanda wanted to put on the label was entrainment
14 as measured by a biomarker, correct?

15 **A.** Yes.

16 **Q.** And what happened is that FDA rejected reliance on a
17 biomarker, correct?

18 **A.** It's my opinion they rejected entrainment as well.

19 **Q.** But you don't disagree that throughout the process,
20 the clinical data were treated as clinical results from
21 entrainment, correct?

22 **A.** The only conclusion I can make is FDA -- if the FDA
23 believed that the entrainment was the indication of the
24 drug, they would have put it in the labeling. Because
25 even if they rejected the biomarker, they could have had

~~Jaskot~~ - Cross

1 entrainment associated with the clinical benefit of
2 approved nighttime sleep and daytime naps.

3 **Q.** So assume that a sleep physician reads the label and
4 reads it the way Dr. Combs does, which is that the
5 clinical data and the instruction to take it once daily
6 before bedtime and to skip the dose if you miss a dose,
7 and the notion that it may take a while until it starts to
8 work because of the cyclical nature of the disorder, the
9 physician reads all that and thinks, oh, this is working
10 by entrainment, FDA never said anything contrary to that,
11 did they?

12 **A.** There are many drugs that have those same directions
13 which are not meant for entrainment or Non-24. They are
14 not uncommon directions.

15 **Q.** I'm sure that was an answer to a question, and I'm
16 grateful to you for it. But I don't think it was the
17 answer to mine.

18 So at no point in time in the history of the
19 prosecution or application for tasimelteon did FDA ever
20 say that those are not evidence of entrainment, correct?

21 **A.** I believe we went through this semantics in our
22 deposition as well. There are many things that the label
23 does not say. There's a universe of things that the label
24 does not say, but it doesn't speak to why they are not
25 said.

Jaskot - Cross

1 Q. Speaking of your deposition, which we haven't yet,
2 it's outside your area of expertise to tell this Court
3 anything about what a doctor would learn from reading the
4 final label, correct?

5 A. That is true.

6 Q. One last quick topic.

7 In his opening statement, Mr. Coblentz drew a
8 distinction between drugs that are approved because they
9 treat the symptoms of the disease and drugs that are
10 approved because they treat the underlying cause.

11 Were you here for opening statements?

12 A. Yes.

13 Q. And you heard him differentiate fluvoxamine for
14 insomnia from Ambien for insomnia, correct?

15 A. Yes.

16 Q. Ambien being the symptomatic relief, correct?

17 A. Yes.

18 Q. The implication was that Hetlioz was approved for
19 treating the symptoms of Non-24, not the underlying cause.

20 Do you agree that FDA approved tasimelteon for
21 symptomatic relief?

22 A. Yes.

23 Q. Isn't it a fact that from the very first meeting, all
24 the way to the end, FDA's position was that you have to
25 treat the underlying cause and that symptomatic relief

Jaskot Redirect

1 would not be enough?

2 **A.** Well, the underlying cause is basically the blindness
3 which, unfortunately, there's no cure for.

4 **Q.** It's your contention -- okay. That's a very
5 important admission, and I'm really grateful to you for
6 it.

7 When you say that tasimelteon doesn't treat the
8 underlying cause of Non-24, you are referring to the
9 blindness. We can all agree that it doesn't treat
10 blindness. But that's what you mean by the underlying
11 cause, just to be clear.

12 **A.** That's my nonmedical, professional assessment of what
13 causes it. I think we've talked about the non- -- I
14 forget the term.

15 **Q.** One last question.

16 In your expert report, you had some opinions about
17 the drug-drug interaction patents. You didn't mention
18 them today in your direct, correct?

19 **A.** That's correct.

20 **MR. STONE:** I have no further questions.

21 **MR. LUKAS:** Very brief redirect for Ms. Jaskot.

22 **THE COURT:** Go ahead.

23 REDIRECT EXAMINATION

24 **BY MR. LUKAS:**

25 **Q.** Ms. Jaskot, we're almost done.

Jaskot Redirect

1 You were asked quite a few questions about the use of
2 the surrogate endpoint entrainment; is that right?

3 Do you remember that?

4 **A.** Yes, yes.

5 **Q.** Is it your testimony that entrainment itself was the
6 surrogate endpoint that was being proposed by Vanda and
7 that's how FDA understood it?

8 **A.** Yes.

9 **Q.** And was that endpoint rejected?

10 **A.** Yes, it was.

11 **Q.** In terms of the PTX-263, you were asked some -- to
12 review some commentary from FDA.

13 Do you remember that?

14 **A.** Yes.

15 **Q.** In your -- based on your experience and understanding
16 of the documents reviewed, which controls the information
17 that goes into the FDA label? Is it the FDA reviewer's
18 commentary, or is it the regulations from the FDA?

19 **MR. STONE:** Objection, Your Honor. Just as a
20 ground rule, how wide can we lead on redirect?

21 **THE COURT:** Well, the ground rule is it's based
22 on what happened at cross.

23 **MR. STONE:** Oh, I don't mean subject matter. I
24 mean, the questions themselves. Of course he can go
25 into -- I didn't mean the subject matter. I meant are we

Jaskot Redirect

1 allowed to lead on redirect?

2 **THE COURT:** So you are objecting on leading?

3 **MR. STONE:** I'm asking -- merely asking whether
4 it's sauce for the goose and sauce for the gander in which
5 case, I won't. That's fine. As long as it is acceptable
6 to the Court, we'll do it, too.

7 **THE COURT:** Well, it depends.

8 **MR. STONE:** Okay. In that case, I will reserve
9 the objection, Your Honor.

10 **THE COURT:** There's some discretion, right? I
11 mean, if it's going to be an important point, I'm going to
12 sustain a leading objection. If I think it's going to be
13 unfair, right, if I think somebody is trying to put words
14 in a witness' mouth, so -- but I don't have an objection
15 so I can't rule on it.

16 **MR. STONE:** Thank you, Your Honor.

17 **BY MR. LUKAS:**

18 **Q.** Do you recall the question, Ms. Jaskot?

19 **A.** Yes.

20 **Q.** Would you like to answer it?

21 **THE COURT:** I don't.

22 **MR. LUKAS:** So would you like me to ask it
23 again, Your Honor?

24 **THE COURT:** Yeah. Why don't you.
25

1 **BY MR. LUKAS:**

2 **Q.** So you reviewed PTX-263. There was some commentary
3 from FDA at various meetings.

4 Do you remember that?

5 **A.** Yes, I do.

6 **Q.** Does that commentary control what goes into the
7 FDA-approved label?

8 **A.** No, it does not.

9 **Q.** What controls -- what goes into the FDA-approved
10 labels?

11 **A.** It's the data that's submitted to the FDA, and
12 they're guided by federal regulation as to what goes in
13 the label.

14 **Q.** All right. Thank you.

15 **MR. LUKAS:** I have no further questions.

16 **THE COURT:** All right. Just give me a second.
17 Okay. Thank you.

18 **MR. ROZENDAAL:** So, your Honor, next up we have
19 two witnesses by video deposition. And after that we'll
20 be calling our non-infringement expert Dr. Winkelman.

21 Each of the videos is approximately 15 minutes.
22 So we could do them now, we could them after lunch, we
23 could do one now and one later.

24 **THE COURT:** Well, let's do one now and then
25 we'll see how long it really goes.

Dressman Video Clip

1 **MR. ROZENDAAL:** Very well. Then defendants
2 call --

3 **THE COURT:** By that I mean, might be 15 minutes
4 that's easy to watch, might be 15 minutes that's very
5 tedious to watch. So that could drive the decision, that
6 would be great.

7 **MR. ROZENDAAL:** I think you'll find there's
8 some good stuff in here, Your Honor.

9 **THE COURT:** Okay.

10 **MR. ROZENDAAL:** The nine minutes that we put in
11 are great.

12 So we call as our next witness
13 Dr. Marlene Dressman by video deposition. She is the
14 former vice president in charge on the clinical program at
15 Vanda Pharmaceuticals. And she is the first named
16 inventor on the four method of treatment patents, the
17 '604, '829, '910 and '487 patents.

18 (Video played.)

19 **"Q.** Could you please state your full name for the record?

20 **"A.** Marlene Michelle Dressman.

21 **"Q.** Would you say that you were primarily in charge of
22 communications with the FDA concerning the Hetlioz NDA?

23 **"A.** I was the direct contact for the Hetlioz project to
24 the FDA.

25 **"Q.** I see. So the average patient who had gone from

Dressman Video Clip

1 sleeping 3.3 hours to 4.3 hours on their worst 25 percent
2 nights of sleep, would you consider that to be
3 entrainment?

4 **"A.** Not by just measuring increases in sleep of one hour.
5 No, I wouldn't call that entrainment. That was a -- I
6 would say that that was an expected product about sleep.
7 What was important, the reason that we were focused on
8 sleep is that patients don't know necessarily when they're
9 entrained because they don't know when their melatonin is
10 peaking. And for it to be from a regulatory perspective,
11 what the patient complains about is a sleep problem.

12 **"Q.** So was there a disagreement between Vanda and the FDA
13 concerning the primary endpoint of Study 3201?

14 **"A.** Initially, there was, but they did approve their
15 marketing application based on the data from the study
16 with this primary endpoint.

17 **"Q.** Could you elaborate a little bit on the nature of the
18 initial disagreement between the FDA and Vanda?

19 **"A.** The FDA wanted a endpoint that was something that the
20 patient would clinically be able to measure them -- you
21 know, a clinically reported measurement, rather than a
22 biomarker. The issue was they didn't want a biomarker,
23 because they wanted something that was relevant to the
24 patient.

25 **"Q.** And so did the FDA want the primary endpoint to be a

Dressman Video Clip

1 clinical endpoint, as opposed to a biomarker?

2 "A. Yes. Because they had not been -- it had not been
3 validated; it wasn't a validated biomarker. There's a
4 formal process that a biomarker needs to go through to be
5 validated.

6 "Q. And it looks like that in the tasimelteon arm of the
7 study, 22 out of 40 patients met that LQ-nTST threshold
8 that we were just discussing; is that correct?

9 "A. Yes.

10 "Q. And do you recall, from our discussion earlier, how
11 many of the 40 patients in the tasimelteon arm of the SET
12 study were entrained?

13 "A. Eight out of -- well, we just looked at it, right?
14 It's 20 percent.

15 "Q. And so fair to say there were at least some patients
16 who had a clinically meaningful increase in their LQ-nTST
17 average, but were not entrained?

18 "A. That's correct.

19 "Q. And so those patients' non-24, had been treated,
20 correct?

21 "A. They were not entrained, but they were sleeping
22 during the nighttime. They had some improvement in sleep.

23 "Q. And would you consider that to be successful
24 treatment of their Non-24?

25 "A. The situation is that -- the reason that we did the

Dressman Video Clip

1 composite scale and why entrainment is important was, just
2 depending on when we measured them. So if they're a very,
3 very slow -- let's say, we were following someone for a
4 year. If they're a very fast circadian clock, they're
5 going to cycle through multiple times and we'll see them
6 cycling through the different phases. But you could also
7 imagine a person who's very slow, just delaying a minute
8 or two a day. Then during the period of our assessment of
9 them, we might just be following them during -- when
10 they're in the period that would be ideal. So it might
11 look like they're sleeping well, but we didn't see a full
12 cycle. So I think it's -- it's just a chance data, you
13 know, when you -- when you evaluated them.

14 "Q. I'll now hand you what has been previously marked as
15 Defendant's Exhibit 85. And this is a document bearing
16 Bates Number VNDHTLZ 02456066. Do you recognize this
17 document, Dr. Dressman?

18 "A. Yes.

19 "Q. What is it?

20 "A. It's the assessment of BMS-214778 for end licensing.

21 "Q. And so is it fair to say that BMS developed
22 tasimelteon for insomnia based on the over-the-counter use
23 of melatonin to treat sleep disorders in populations such
24 as shift workers, blind persons, and travelers suffering
25 from jet lag?

Dressman Video Clip

1 **"A.** This is an interpretation that Vanda made of BMS's
2 strategy. I don't know for certain what their strategic
3 plans were. This was our interpretation.

4 **"Q.** The next sentence states there's extensive literature
5 demonstrating the ability of melatonin to phase advance
6 circadian rhythms. Is that sentence accurate?

7 **"A.** That's what the document says.

8 **"Q.** Okay. I will now hand you what's been previously
9 marked as Defendant's Exhibit 93. Do you recognize this
10 document, Dr. Dressman?

11 **"A.** Yes.

12 **"Q.** Could you read that sentence, please?

13 **"A.** For many of the important design elements of
14 VP-VEC-1623201, Vanda drew on the previous experience from
15 controlled trials of melatonin in Non-24 sleep-wake
16 disorder in the blind.

17 **"Q.** And VP-VEC-1623201, that's the SET study, correct?

18 **"A.** That's correct.

19 **"Q.** And so for many of the important design elements of
20 the SET study, Vanda drew on previous experience from
21 controlled trials of melatonin in non-24 in the blind?

22 **"A.** Vanda used the literature that was available at the
23 time to help inform the safety and efficacy design of the
24 study SET.

25 **"Q.** For the record, Exhibit 114 is an e-mail bearing

Dressman Video Clip

1 Bates Number VNDHTLZ-02021394. Exhibit 115 was produced
2 as an attachment to Exhibit 114. It bears Bates
3 Number 02021397. Exhibit 116 was also produced as an
4 attachment to the Exhibit 114, and it bears Bates
5 Number VNDHTLZ-02021407.

6 Dr. Dressman, Exhibit 114 is an e-mail that's sent by
7 you to Eve van Cauter; is that correct?

8 "A. Uh-huh.

9 "Q. And the next sentence states: The papers by Hack and
10 Sack helped inform the design of our studies. Do you see
11 that?

12 "A. Yep.

13 "Q. And those papers by Hack and Sack, are those the two
14 documents that are before you as Exhibits 115 and 116?

15 "A. Yep. Yes.

16 "Q. These papers by Hack and Sack, did they help inform
17 the design of the Vanda's studies of tasimelteon to treat
18 non-24?

19 "A. In some ways, they gave us information. In one way,
20 what was -- they demonstrated was how important the dose
21 could be to entrainment. They didn't -- they didn't
22 clarify what was the appropriate dose. So you can see
23 that in the paper by Sack, they started off with
24 10 milligrams to try to entrain patients until it was
25 achieved, and then they reduced it to 0.5 MGS per day;

Dressman Video Clip

1 whereas in the other ones, they started with
2 0.5 milligrams per melatonin. And so it wasn't -- it
3 wasn't clear. And I think they -- one gave an hour
4 before -- where was it? One hour before their preferred
5 bedtime for three-to-nine weeks. I think the other one
6 might have given it a half-hour before. So there was --
7 there -- it wasn't clear what was the critical components
8 of time and dose. And then there's another study that's
9 not shown here, that -- that's -- Dr. Lewy, I believe, is
10 an author on that, that showed that a certain treatment
11 wasn't very efficacious. And these are -- if you'll
12 notice, these are really small studies as well. Six
13 patients in the New England Journal and only a few
14 patients in the other ones. Ten.

15 **"Q.** And so these authors concluded that .5 milligrams
16 melatonin administered daily is effective in entraining
17 free-running circadian rhythms in blind patients?

18 **"A.** That's what that sentence says.

19 **"Q.** When I asked if the papers by Hack and Sack helped to
20 inform the design of your studies, you -- instead of
21 saying yes or no, you've said that they were part of the
22 body of literature that you were looking at when you were
23 doing these studies. And I'm trying to determine what the
24 difference is between those two things. So could you
25 elaborate on that a little bit?

Dressman Video Clip

1 **"A.** The difference between what two things?

2 **"Q.** Between the Hack and Sack papers helping to inform
3 the design of the studies, and between those papers
4 forming part of the body of literature that you were
5 looking at.

6 **"A.** The -- I think I'm trying to make the point that
7 there's -- it's misleading to think that this is the only
8 thing that went into designing the -- the protocol. And
9 the way that you've been wording things sounds as if
10 you're trying to imply that this is the only thing that
11 was derived -- driving the design of the protocol. And
12 I'm just making the point that there was a lot of
13 uncertainty at this point when we designed the studies
14 around how tasimelteon -- what would be the appropriate
15 dose, whether it would be able to entrain, what was the
16 appropriate time of entrainment, and how long you would
17 need to treat, when would you start treating the patients
18 within their cycle. There were a lot of unknowns that we
19 needed to test to understand what would be the appropriate
20 method to treat patients who had non-24 sleep-wake
21 disorder.

22 **"Q.** I will now hand you what will be marked as
23 Defendant's Exhibit 121. This is an e-mail bearing Bates
24 Number VNDHTLZ-00019621. Who is the author of the top
25 e-mail in the chain?

Dressman Video Clip

1 "A. Myself.

2 "Q. And who are the recipients?

3 "A. Steve Lockley and Gabrielle Thibodeau.

4 "Q. If you turn to the next page of the document, there
5 is a message from Steve Lockley to Gabrielle Thibodeau and
6 you, dated Tuesday, June 5, 2012. Do you see that?

7 "A. Yes.

8 "Q. Could you read that paragraph, please?

9 "A. (Reading): None of them acknowledge that melatonin
10 can entrain the circadian rhythm of blind people --
11 Lockley, et al., 2000. Sack, et al., 2000 -- which is
12 what led to the thinking that tasi might be effective.

13 "Q. And the next sentence, too, please.

14 "A. Oh, I'm sorry. (Continues reading): It's hard to
15 shy away from the fact -- even though I understand why,
16 hard to shy away from that fact.

17 "Q. Later in that paragraph that you -- that you read
18 earlier, it states, 'which is what led to the thinking
19 that tasimelteon might be effective.' Is it true that the
20 fact that melatonin can entrain the circadian rhythms of
21 blind people is what led to the thinking that tasimelteon
22 might be effective?

23 "A. As we've discussed previously, multiple times, there
24 was a whole body of evidence, including melatonin
25 research, including the Lockley and Sack papers, that were

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1 used to help design and inform our clinical studies, but
2 it was -- it -- it was a broad body of data and
3 literature.

4 "Q. Do you recall your earlier testimony about the SET
5 study report, which is Exhibit 81, Defendant's Exhibit 81?

6 "A. Yes.

7 "Q. And do you recall testifying that in that study, you
8 looked for various markers of entrainment, including
9 biomarkers and clinical endpoints?

10 "A. Yes.

11 "Q. What were those clinical endpoints?

12 "A. Measures of sleep, LQ-nTST, so the lower quartile of
13 nighttime total sleep time. And UQ-dTSD, so the upper
14 quartile of daytime total sleep time.

15 "Q. I believe you were shown the Hetlloz label, which
16 is -- oh, my goodness -- Defendant's Exhibit 124. Does
17 that Hetlloz label also discuss those same clinical
18 endpoints in Section 14?

19 "A. Yes, it does.

20 "Q. Have you ever treated a patient with non-24?

21 "A. No, I have not.

22 "Q. Have you ever treated a patient with a circadian
23 rhythm disorder?

24 "A. I have not.

25 "Q. Have you treated -- have you ever treated a patient

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1 with tasimelteon?

2 "A. No, I have not.

3 "Q. Have you ever treated a patient with melatonin?

4 "A. No, I have not.

5 "Q. Do you know how a clinician would assess entrainment
6 of a patient?

7 "A. I do not.

8 "Q. During the clinical trials, what was considered a
9 marker of success for a patient with non-24 on a regimen
10 of 20 milligrams of tasimelteon once a day before bedtime?

11 "A. A positive efficacy outcome would be a measure of
12 entrainment as measured by 6-sulfatoxymelatonin, as well
13 as entrainment of cortisol, as well as improvements in
14 LQ-nTST, and improvements in UQ -- the lower quartile
15 dTST, as well as the composite score, which measured all
16 of those -- those as well as the median. It measured the
17 two nighttime and daytime sleep, and the median score, as
18 well as the clinician's global impression of change.

19 **THE COURT:** All right.

20 **MR. ROZENDAAL:** Your Honor, I realize that I
21 neglected to offer a copy of the transcript to the Court
22 and the staff.

23 Would you like to have it now or --

24 **THE COURT:** You can just hand it up, sure.

25 **MR. ROZENDAAL:** Sorry. Yes. I'm handing up

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1 the designation and the exhibits, not the entire
2 transcript.

3 **THE COURT:** Okay.

4 All right. We'll break for lunch.

5 Before you do, just a couple quick questions.

6 So, you know, there's been lots of references
7 to the draft label and then questions and -- well, there's
8 no proof that it went to FDA.

9 So is the bottom line, we don't have the FDA
10 files whether the draft -- or Vanda files -- whether a
11 draft was given?

12 Is that the bottom line?

13 **MR. ROZENDAAL:** I believe Dr. Polymeropoulos
14 testified that it went to FDA.

15 **MR. STONE:** Well, then...

16 **THE COURT:** Because I just forget. I mean
17 like, the reason why I'm moving, like, well, does it
18 matter, because you are proposing entrainment, so...

19 **MR. STONE:** And I think -- here's where I think
20 that is, Your Honor. There is certainly no dispute that
21 Vanda was seeking approval throughout the process based on
22 the biomarker and all the things that we talked about.

23 On the stand, Dr. Polymeropoulos testified that
24 he doesn't actually know whether that version went. He
25 was shown deposition testimony in which he testified that

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1 he thinks it did. That's where the record stands.

2 We, obviously, at some point, submitted a draft
3 label. I don't think they've actually proven up that it
4 is this draft label.

5 **THE COURT:** And that's my point, right.
6 Because where I am is basically, we don't have the record
7 evidence that any of the draft labels -- because I think
8 there's been more than one that have been identified --
9 actually went to the FDA. We don't have a proof of that,
10 right?

11 **MR. STONE:** Correct.

12 **THE COURT:** But it's an inference I would be
13 free to draw.

14 **MR. STONE:** I think -- I don't mean to quibble
15 whether the Court is free to draw the inference. My point
16 is simply, I think to the extent we're fencing about
17 individual words in it, we don't know if that document
18 went in. The notion that Vanda asked to have that on the
19 label as part of the approval process, we're not
20 disputing.

21 **THE COURT:** Well, the "that" there may be some
22 dispute for what "that" means.

23 **MR. STONE:** I think there may be, and I think
24 that that's their burden. But to the extent that they
25 want to argue to this Court that a physician would, A,

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1 somehow know what's --

2 **THE COURT:** Why is it their burden?

3 **MR. STONE:** It is our burden to prove

4 infringement from the label as it exists.

5 **THE COURT:** Fair. Right.

6 **MR. STONE:** The defendants are trying to create

7 a suggestion that it matters what's not in the label from

8 the drafting history. I think that's legally wrong. But

9 to even mount the argument that it should matter, they

10 have to prove what went to FDA. That's an issue they've

11 introduced.

12 I don't have to engage what's not in the label.

13 I have to start with the label as it exists and put on

14 evidence for how someone will use it, which I think we've

15 done.

16 **THE COURT:** So it's an interesting issue, now

17 that I think about it. I think we all agree you look at

18 the label. And the next question is: What does the label

19 mean? And you want to limit the consideration of what the

20 label means to what a doctor, prescribing physician, would

21 take from it.

22 **MR. STONE:** Yes, Your Honor. And I think that

23 there is --

24 **THE COURT:** And what they want to do is, I

25 think they're going to dispute that. I'm going to guess

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1 they're going to have a -- a prescribing physician that's
2 going to say, your prescribing physician has no idea what
3 he's talking about, right? That's probably what he's
4 going to say.

5 **MR. STONE:** I think that might be right.
6 Although his deposition will be a challenge for him, but
7 yes.

8 **THE COURT:** Okay. But it begs the question,
9 well, do we -- can we consider extrinsic evidence to
10 decide what the FDA meant when it issued the label?

11 And I mean, it is a very, you know -- at least
12 at first blush, a pretty telling fact that your client was
13 afraid to use the word "entrainment" in marketing this
14 drug.

15 **MR. STONE:** I take that point. I would point
16 out that that document says they can use the word
17 "synchronize," which is the Court's construction of the
18 word "entrainment." But we can -- that will obviously be
19 an issue in the case.

20 I would call to the Court's attention in that
21 regard, *AstraZeneca versus Apotex*, 633 F.3d 1042 from
22 2010. What happened in that case, is that at the -- the
23 case was about whether patents that required once daily
24 dosing of a medicine, the label called for twice daily
25 dosing but to titrate down once it worked.

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1 And the question is: Is that an instruction to
2 eventually use once daily dosing? Federal Circuit says,
3 Yes.

4 But Apotex had gone to FDA and said, we don't
5 want to put that language on, because that's once daily
6 dosing. FDA said, no, it isn't.

7 And when it goes to the Federal Circuit, the
8 Federal Circuit says, it's not -- quoting directly: The
9 FDA is not the arbiter of patent infringement issues and
10 rejects FDA's view as to what the label means.

11 **THE COURT:** Is that an ANDA case?

12 **MR. STONE:** It is ANDA.

13 **THE COURT:** Okay. And it is looking at the
14 label?

15 **MR. STONE:** And it is looking at the label.
16 And what it is saying in that passage is, it actually
17 doesn't matter what FDA thinks the language in the label
18 means. What matters is what's in the label and what does
19 a doctor think it means.

20 And so I think Your Honor has correctly framed
21 the question, which is what does the label tell a
22 physician. I'm sure there will be a dispute between the
23 experts. I'm sure you're right about that.

24 I think -- as Ms. Jaskot, I think, fairly said
25 lots of things aren't in the label. You know, the fact

1 that I am married isn't in the label, but I still am.

2 But I think it may or may not matter what Vanda
3 was trying to achieve on the simple point of the draft
4 label that we've been discussing. To the extent the
5 argument is FDA was looking at those particular words,
6 there is no evidence of that. In the larger context --

7 **THE COURT:** Lost you. Sorry. To the extent?

8 **MR. STONE:** That their argument that this is
9 the draft label that FDA rejected, they haven't proven
10 that up. On the other hand, the general notion that that
11 was the conversation, we're not disputing.

12 **THE COURT:** All right. Okay.

13 **MR. ROZENDAAL:** Your Honor, just to -- first of
14 all, just to respond to that briefly.

15 We obviously think that the back and forth
16 between Vanda and the FDA is highly probative of what
17 physicians working in this field understand the words of
18 the label to mean. And the ones that are -- that they
19 tried to get in and didn't get in, I think that's a strong
20 inference that people working in the field would
21 understand that the missing words don't mean the same
22 thing as the words that are actually there.

23 I also just wanted to, as a housekeeping
24 matter, finish up the exhibits that were used in the depo
25 designation. So we would -- defendants would move for the

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1 admission of JTX- 120, DTX- 31, DTX- 323, DTX- 326, and
2 DTX- 331.

3 **MR. STONE:** No objection to any of those,
4 Your Honor.

5 **THE COURT:** All right. They are admitted.
6 All right. We will be back. Will 1:00 work?

7 **MR. ROZENDAAL:** Works for defendants,
8 Your Honor.

9 **MR. STONE:** Works for plaintiff.

10 (Whereupon, a recess is taken.)
11

12 **THE COURT:** So apparently a member -- well, an
13 arbitrager, I think, on behalf of the public, though, he
14 handed his card to my deputy and said that, speaking on
15 behalf of the public, we ought to have more than 30-minute
16 lunches, so can he go out to eat.

17 And so I won't name the individual. What I
18 will say is: I think the public gets its tax money out of
19 us. It gets the benefit of it, and we're doing half-hour
20 lunches at trials, so we can get through our cases.

21 All right. That said, Counsel.

22 **MR. ROZENDAAL:** Thank you, Your Honor.

23 Defendants call as their next witness by video
24 deposition, Dr. John Feeney, who is the former chief
25 medical officer of Vanda, and a named inventor on the

1 '604, '829 and '910 patents.

2 Your Honor should have a copy of these excerpts
3 on the bench.

4 **THE COURT:** I do. Thank you.

5 (Video clip played.)

6 "Q. Good morning, Dr. Feeney. Could you please state
7 your full name for the record.

8 "A. John Joseph Feeney.

9 "Q. I'll now hand you what we'll mark as Defendant's
10 Exhibit 86. Are you familiar with this article?

11 "A. I am.

12 "Q. So based on this, was it known by at least 2008 that
13 the tasimelteon may have therapeutic potential for
14 transient insomnia and circadian rhythm sleep disorders?

15 "A. That's what it says here.

16 "Q. And based on this, at least by 2008, was it known
17 that you could administer 20 milligrams of tasimelteon to
18 a patient 30 minutes before bedtime?

19 "A. Yes.

20 "Q. And so at least as of 2008, it was known that
21 exogenous melatonin can shift sleep time and hormones and
22 increase sleep propensity, particularly during times of
23 day when endogenous melatonin production is low?

24 "A. That's what it says here.

25 "Q. Have you ever used melatonin to treat any type of

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1 sleep disorder in your clinical practice?

2 "A. No.

3 "Q. Have you ever used other medications to treat any
4 type of sleep disorder in your clinical practice?

5 "A. Yes.

6 "Q. Do you agree that as of 2010, there was strong and
7 unequivocal evidence for the chronobiotic properties of
8 melatonin?

9 "A. Do I agree with the strong evidence or unequivocal
10 evidence for melatonin?

11 "Q. Correct.

12 "A. You know, to say strong, I -- I can barely remember
13 any of the evidence, right at the minute -- at this
14 minute. I don't doubt that the experts would say yes to
15 that.

16 "Q. What was known about the treatment of circadian
17 rhythm disorders with tasimelteon as of 2010?

18 "A. Well, 2010, there were the -- I think it was 2101 and
19 3101 had been published. They were the phase advance --
20 the sleep -- the -- advancing the sleep cycle in those
21 patients. You showed the paper, the Lancet paper earlier.
22 So from one of those studies, it was shown that you could
23 shift the onset of melatonin earlier by the administration
24 of tasimelteon.

25 "Q. Was it known by 2010 that tasimelteon has a high

1 affinity for the same receptors as melatonin does?

2 "A. Are you asking, was it known that it was a melatonin
3 agonist?

4 "Q. Was it known that it had a high affinity for the same
5 receptors as melatonin?

6 "A. Well, I kind of forget the exact binding profiles of
7 melatonin side by side with tasimelteon, but it was -- the
8 binding profile of tasimelteon was known, I believe.

9 "Q. So that's not necessarily equivalent to entrainment?

10 "A. An improvement in sleep?

11 "Q. Correct.

12 "A. No.

13 "Q. And you could improve someone's sleep and not entrain
14 them?

15 "A. Yes.

16 "Q. I'll now hand you what will be marked as Defendant's
17 Exhibit 91, and it's a clinical study protocol for Study
18 VP-VEC-1621111; is that correct?

19 "A. Yes.

20 "Q. Do you recall the purpose of this clinical study.

21 "A. To investigate the -- to investigate the effects of
22 concomitant administration of fluvoxamine with the PK of
23 tasimelteon.

24 "Q. Why did Vanda want to investigate the effects of
25 concomitant administration of fluvoxamine and tasimelteon?

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1 **"A.** I will say that 1A2's involved in -- potentially
2 involved in the metabolism of tasimelteon, and we were
3 studying what effect an inhibitor like fluvoxamine would
4 have on the plasma levels of tasimelteon.

5 **"Q.** Is fluvoxamine a standard CYP1A2 inhibitor to use in
6 studies of this type?

7 **"A.** Yes, I believe it is.

8 **"Q.** If you could turn, please, to Page 18 of this
9 document, which ends in Bates Number 283.

10 **"A.** Okay.

11 **"Q.** And underneath the Rationale section, there's a
12 section called 'Study Rationale,' and it states: In vitro
13 studies with CDNA-derived cytochrome P450 isozymes have
14 shown that tasimelteon is metabolized by four cytochrome
15 P450s: CYP1A1, CYP1A2 and CYP2C9 and CYP2D6. Do you see
16 that?

17 **"A.** I do.

18 **"Q.** And could you read those two sentences out loud,
19 please?

20 **"A.** (Reading): A 5-milligram dose will be used in the
21 study instead of the 20-milligram dose, which is the dose
22 being tested in the Phase III clinical studies because
23 tasimelteon is primary metabolized by 1A2. Ramelteon,
24 another melatonin receptor agonist, which is also
25 primarily metabolized by 1A2, had an increase in the AUC

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1 of about 190 fold, and in Cmax of about 70 fold with
2 coadministration with fluvoxamine.

3 "Q. Because performing a study like this to test possible
4 drug-drug interaction is --

5 "A. Yes.

6 "Q. -- a routine part of developing a new drug?

7 "A. Yes.

8 "Q. I understand. You can put that aside. I'll now hand
9 you what will be marked as Defendant's Exhibit 93. Are
10 you familiar with this document, Dr. Feeney?

11 "A. I think I am. I'm going to say yes.

12 "Q. If you turn to the sixth page of the document, ends
13 in Bates Number 549, do you see it says 'Sponsor
14 attendees'?

15 "A. Yes.

16 "Q. And you're listed as one of the attendees, correct?

17 "A. Yes.

18 "Q. And that means you were attending this meeting on
19 behalf of Vanda Pharmaceuticals?

20 "A. Yes.

21 "Q. Do you recall the details of the meeting, what was
22 discussed?

23 "A. Not so much.

24 "Q. If you turn to Page 3 of that document, please,
25 ending in Bates Number 546. If you could read out loud,

1 please, the first sentence of the third paragraph, which
2 begins, 'For many of the important.'

3 "A. For many of the important design elements of 3201,
4 Vanda drew on the previous experience from controlled
5 trials of melatonin in non-24 in the blind.

6 "Q. Is that sentence accurate?

7 "A. I would say for some of the important design
8 elements, we drew on previous experience. For many, we
9 had to hash out many details working with our consultants.

10 "Q. So this statement that for many of the important
11 design elements of 3201, Vanda drew on the previous
12 experience from controlled trials of melatonin in non-24
13 sleep-wake disorder in the blind, you would disagree with
14 that statement?

15 "A. I would say, you know, it was -- it was an
16 evolving -- the development program was evolving. We did
17 draw on some of the design elements from previous trials
18 of melatonin in non-24. Many more of the design elements
19 either came from our own experience in drug development or
20 from extensive, extensive discussions with our
21 consultants, our sleep experts.

22 "Q. And so the sentence as written, do you believe that
23 that's inaccurate?

24 "A. I think the answer is yes, I kind of do disagree with
25 it.

1 "Q. Who at Vanda drafted the document?

2 "A. Who drafted it? I would guess the people listed in
3 Item 10 contributed the most to it.

4 "Q. And you're one of those individuals listed in
5 Item 10, correct?

6 "A. Yes.

7 "Q. Did you play a role in drafting this document?

8 "A. I presume I did.

9 "Q. And this document went to the FDA, correct?

10 "A. Yes.

11 "Q. I'm going to hand you what will be marked as
12 Defendant's Exhibit 94. This is an e-mail from
13 Rosa Torres, dated Thursday, the 12th of November, 2009;
14 is that correct?

15 "A. Yes.

16 "Q. And you're listed as a recipient of this e-mail; is
17 that correct?

18 "A. Yes.

19 "Q. I'll now hand you what will be marked at Defendant's
20 Exhibit 95. If you turn back to Exhibit 94, the first
21 sentence states: Please find attached the summaries for
22 the latest studies done using melatonin in subjects with
23 non-24 sleep-wake syndrome. Do you see that?

24 "A. Yes.

25 "Q. Is the attachment the summaries of the latest studies

1 done using melatonin in subjects with non-24 hour
2 Sleep-wake disorder?

3 "A. I see two listed here. If those are the only two, I
4 would say yes.

5 "Q. And the next sentence of the e-mail states: For what
6 I read, I think that it is fine to dose subjects
7 regardless of their circadian phase and most subjects if
8 not all, would eventually become entrained. Do you see
9 that?

10 "A. Yes.

11 "Q. And so is it fair to say that Ms. Torres is basing
12 her decision on dosing on the outcomes of these studies in
13 melatonin?

14 "A. It sounds like she's making her recommendation based
15 on these two trials.

16 "Q. And so she's making her recommendation regarding the
17 tasimelteon studies based on studies done using melatonin?

18 "A. She is. I'll add, half as a question, I believe when
19 the trials were -- when the trial was actually done, it
20 was done a different way.

21 "Q. And I believe you testified earlier that with respect
22 to Exhibit 84, the RE604 patent, you are named as an
23 inventor, correct?

24 "A. Yes.

25 "Q. And then if you -- if you follow that line along, it

1 says: Following a daily sleep period of approximately
2 seven-to-nine hours. What is a daily sleep period of
3 approximately seven-to-nine hours?

4 "A. It's a consolidated period of sleep lasting
5 seven-to-nine hours, that occurs in kind of the socially
6 acceptable time frame for that consolidated sleep period.

7 "Q. If a patient were to sleep from 1:30 a.m. to
8 5:30 a.m., would that constitute a sleep period of
9 approximately seven-to-nine hours?

10 "A. No.

11 "Q. Why not?

12 "A. Because that's four hours. That's less than seven.

13 "Q. Have you ever treated a patient with non-24?

14 "A. No.

15 "Q. Have you ever treated patients with tasimelteon?

16 "A. No.

17 "Q. Have you ever treated patients with melatonin?

18 "A. No.

19 "Q. Have you ever treated patients with circadian rhythm
20 disorders?

21 "A. I can't remember specifically.

22 "Q. If you had, how long ago would that have been?

23 "A. It would have been many years ago.

24 "Q. Approximately how many?

25 "A. Fifteen or more.

Feeney Video Clip

1 **"Q.** Have you -- strike that. Do you remember testifying
2 about the meaning of the term 'daily sleep period of
3 seven-to-nine hours' in some of the claims?

4 **"A.** Yes.

5 **"Q.** When you testified about that term, was that based on
6 anything you read or recalled about the patent
7 specifications?

8 **"A.** No.

9 **"Q.** Do you know what daily sleep period of seven-to-nine
10 hours means within the context of the patent claims?

11 **A.** No, not really.

12 **MR. ROZENDAAL:** Your Honor, we move the
13 admission of DTX-25, DTX-351, DTX-352 and DTX-353.

14 **MR. KLEIN:** No objection.

15 **THE COURT:** All right. They are admitted.

16 (DTX-25, DTX-351, DTX-352 and DTX-353 admitted
17 into evidence.)

18 **MR. COBLENTZ:** Defendants now call
19 Dr. John Winkelman.

20 **THE COURT:** Okay.

21 **MR. COBLENTZ:** Permission to approach with
22 binders.

23 **THE COURT:** Sure.

24 **THE CLERK:** Please remain standing and raise
25 your right hand. Please state and spell your name for the

1 record.

2 **THE WITNESS:** John Winkelman,
3 W-I-N-K-E-L-M-A-N.

4 John Winkelman, having been called as a witness,
5 having first affirmed or being duly sworn under oath,
6 testified as follows:

7 **THE CLERK:** Thank you. You may be seated.

8 **MR. COBLENTZ:** May I proceed, Your Honor?

9 **THE COURT:** Yes.

10 DIRECT EXAMINATION

11 **BY MR. COBLENTZ:**

12 **Q.** Dr. Winkelman, could you please introduce yourself to
13 the Court.

14 **A.** Yes. My name is John Winkelman.

15 **Q.** And did you help prepare some slides that would
16 assist with your testimony today?

17 **A.** I did.

18 **Q.** Before we get there, I want to talk a little bit
19 about your background.

20 **MR. COBLENTZ:** And if we go to DTX-402,
21 Mr. Brooks, if you could pull that up on the screen.

22 **BY MR. COBLENTZ:**

23 **Q.** Dr. Winkelman, is this a copy of your CV?

24 **A.** Yes, it is.

25 **MR. COBLENTZ:** I'd like to move DTX-402 into

1 evidence.

2 **MR. KLEIN:** No objection.

3 **THE COURT:** All right. It's admitted.

4 (DTX-402 admitted into evidence.)

5 **BY MR. COBLENTZ:**

6 **Q.** Dr. Winkelman, can you summarize your education for
7 the Court, please?

8 **A.** Yes. Thank you.

9 I got my bachelors in psychology from Williams
10 College. Five years later, I completed my Ph.D. in psycho
11 biology from Harvard. And four years after that, I
12 completed my medical degree at Harvard Medical School.

13 **Q.** Can you tell us a little bit about your present
14 position right now?

15 **A.** Yes. I'm a professor of psychiatry at Harvard
16 Medical School, and chief of the Sleep Disorders Clinical
17 Research program at Massachusetts General Hospital.

18 **Q.** Can you tell us a little bit about that research
19 program?

20 **A.** Yes. Absolutely.

21 We study a variety of sleep disorders, insomnia,
22 parasomnia, restless leg syndrome and their relationship
23 to psychiatric illness, neurological disease and general
24 medical disorders. And we look at that from genetic
25 perspectives, all the way up to epidemiologic levels, and

1 perform and are involved in the development of a variety
2 of medications to treat sleep disorders.

3 **Q.** Can you briefly summarize your research that you've
4 done over the years?

5 **A.** Well, I mostly just alluded to that. Research on
6 insomnia, research on restless leg syndrome, on
7 parasomnia. At these various levels, genetic,
8 epidemiologic, clinical trials.

9 **Q.** Do you have experience with circadian rhythm sleep
10 disorder?

11 **A.** Yes, of course. I have been a practicing sleep
12 doctor for 30 years. And every patient I see gets
13 evaluated. I evaluate them for circadian rhythm
14 disorders. I treat patients with a variety of circadian
15 rhythm disorders.

16 **MR. COBLENTZ:** Your Honor, I believe the
17 parties have agreed that Dr. Winkelman is an expert for
18 the purposes of this case.

19 **THE COURT:** All right.

20 **BY MR. COBLENTZ:**

21 **Q.** Now, if we can move to DDX-3.2, please.

22 Now, Dr. Winkelman, did you review the Hetlioz label,
23 which is JTX-28, for the purpose of your opinion?

24 **A.** I did.

25 **Q.** And how about Teva's label, which is JTX-30, did you

1 review it for the purposes of your opinion?

2 **A.** Yes, I did.

3 **Q.** And Apotex's label, which is JTX-33, did you review
4 it as part of your opinion?

5 **A.** Yes.

6 **Q.** Did you compare these labels to one another?

7 **A.** I did.

8 **Q.** Are there any meaningful differences between the
9 labels?

10 **A.** No.

11 **Q.** And given that, can we focus on one of the labels for
12 the purposes of your discussion today?

13 **A.** Absolutely.

14 **Q.** And which label would you like to focus on?

15 **A.** Hetlitz.

16 **Q.** Okay. Now, if we can go to DDX-3.3. I'd like to
17 talk to your -- about your opinion on the entraining term
18 from Claim 3 of the RE604.

19 What is your opinion on that term?

20 **A.** It is my opinion that the defendant cannot induce
21 infringement of the RE604 patent because they do not
22 encourage, recommend, require or promote the use of
23 defendants' products as a method specifically here for
24 entraining a patient.

25 **Q.** And if we move to DDX-3.4. We're looking at the

1 Hetlitz label, which is JTX-28.

2 What does the Hetlitz label say tasimelteon is used
3 to treat?

4 **A.** It's indicated for the treatment of Non-24-hour
5 Sleep-Wake Disorder in adults.

6 **Q.** Now, in your opinion, do the defendants' labels
7 instruct prescribers to entrain Non-24 patients?

8 **A.** No.

9 **Q.** And why is that?

10 **A.** There's no mention of entraining, synchronizing,
11 entrainment, synchronize at any point in the label.

12 **Q.** Now, why doesn't treat Non-24 mean treating the
13 underlying condition?

14 **A.** Well, you can treat the underlying cause or you can
15 treat the symptoms. In medicine, we understand this
16 distinction with patients every day. And -- so I guess I
17 will conclude there.

18 **Q.** If the treatment does not involve entraining patients
19 with Non-24, what does the label tell a physician about
20 the treatment of Non-24 with tasimelteon?

21 **A.** That you can treat the symptoms of Non-24, the sleep
22 disturbance, which is the main reason why patients come to
23 you with this problem. That you can treat the symptoms,
24 the sleep, but doesn't instruct us anything about whether
25 we're entraining patients or not.

1 Q. Do physicians distinguish between approaches that
2 treat the cause of a condition versus those that treat the
3 symptoms?

4 A. Yes, every day. This is what doctors do. We see
5 patients, they come in with a complaint, we try -- we try
6 to treat the cause, if possible. A lot of times, we can't
7 treat the cause. We treat the symptoms.

8 This is just part of medical practice. It's part of
9 everyday life, in fact. You know, I've got -- I've been
10 sitting on these benches for how many hours? Maybe I
11 shouldn't go into this. But I played too much basketball
12 as a kid, and I -- my back hurts. I'm not getting
13 treatment for the cause of that by having disc surgery,
14 I'm treating it with a lot of Advil and I'm treating those
15 symptoms effectively.

16 MR. COBLENTZ: If we go to the next slide.

17 BY MR. COBLENTZ:

18 Q. This is DDX-3.6.

19 And how about patients with insomnia?

20 A. Yes. Well, let's take patients with insomnia come to
21 my office, maybe a quarter of them will have insomnia due
22 to a mood or anxiety disorder. This is not uncommon. I
23 could treat the cause of that mood or anxiety disorder
24 with something like fluvoxamine -- that we'll hear about
25 later, Luvox -- which would treat the underlying

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1 depression, or I could treat their sleep symptoms with
2 something like Ambien or sedating antidepressants like
3 Remeron and I'd be treating the symptoms of sleep
4 disturbance without necessarily treating the underlying
5 cause.

6 **MR. COBLENTZ:** Now, if we could move to
7 DDX-3.7.

8 **BY MR. COBLENTZ:**

9 **Q.** Dr. Winkelman, how does this compare to what we see
10 in defendants' labels versus what is claimed in Claim 3 of
11 the RE604 patent?

12 **A.** Well, the patent, RE604 patent, is directed towards
13 treating the cause of Non-24. The lack of entrainment.
14 The label in distinction discloses symptomatic treatment,
15 treatment of the sleep disturbance that is characteristic
16 of Non-24. These are very distinct.

17 **MR. COBLENTZ:** If we go to DDX-3.8. And,
18 again, we're in JTX-28 --

19 **THE COURT:** Is entrainment the cause of Non-24?

20 **THE WITNESS:** Is lack of entrainment?

21 **THE COURT:** Sorry. Lack of entrainment or a
22 cause?

23 **THE WITNESS:** Well, yes. I mean, they're
24 blind.

25 **THE COURT:** Okay. I wanted to make sure.

1 Thank you. Sorry.

2 **BY MR. COBLENTZ:**

3 **Q.** So if we go to DDX-3.8 here, and looking at JTX-28,
4 which is the Hetlioz label, and we look specifically at
5 the Clinical Study section of the Hetlioz label, does the
6 Clinical Study section reveal symptomatic treatment or
7 treatment of the underlying condition?

8 **A.** Clearly, it demonstrates symptomatic treatment.
9 There's a lot of discussion about sleep, sleep, sleep, but
10 no mention of entraining patients.

11 **MR. COBLENTZ:** And if we go to DDX-3.9.

12 **BY MR. COBLENTZ:**

13 **Q.** What, in the Clinical Studies section of the Hetlioz
14 label causes you to conclude that the label is not
15 directed to entrainment?

16 **A.** Well, if we look at this -- try to use the pointer.

17 If we look at this table here, Table 3, which is
18 really the only data that exists in the label, other than
19 the side affects, we see that all these outcomes here,
20 these endpoints, are all sleep outpoints and endpoints.
21 They talk about more sleep at night, less sleep during the
22 day. That's why.

23 **Q.** Now, let's break this table down from the label here.
24 And what is referred to as Study 1 in the -- in Table 3 of
25 JTX-28?

1 **A.** Study 1, we've heard about this earlier today and
2 yesterday as well. It's the SET study. Table 2 is known
3 as the RESET study.

4 **Q.** And I believe you said "Table 2." You mean Study 2?

5 **A.** I'm sorry. Study 2, yeah.

6 **Q.** Now, what was the design of Study 1?

7 **A.** They took patients with Non-24, investigators did,
8 and did a double-blind placebo-controlled randomized
9 study. They took half the people and gave them Hetlioz,
10 the other half of the people, they gave a placebo.

11 **Q.** And what data is reported in the Hetlioz label about
12 Study 1 here?

13 **A.** Well, we can see here nighttime sleep. And
14 25 percent worst nights increased 50 minutes with Hetlioz,
15 22 minutes with placebo. We look at the daytime naptime,
16 that was decreased by 49 minutes with Hetlioz, and
17 22 minutes with placebo.

18 **Q.** Is there any data on melatonin or cortisol in this
19 part of the label?

20 **A.** No, not at all.

21 **Q.** Now, the data we see here on Table 3 of the Hetlioz
22 label, the data that's reported for Study 2, it's pretty
23 much the same as for Study 1, or the same endpoints; is
24 that correct?

25 **A.** The endpoints are all sleep endpoints. That's all we

1 know.

2 Q. And what is -- briefly, what is the difference
3 between Study 1 and Study 2?

4 A. Study 1, they took patients who were not entrained
5 and gave them drug or placebo. In Study 2, they took
6 patients who were entrained, continued them. It's called
7 a randomized withdrawal study. And either continued this
8 on Hetlioz or switched them over to placebo, blind.

9 Q. Now, the nighttime sleep time that's in Table 3 here,
10 and this daytime naptime that's in Table 3 on the label,
11 does that measure the change in the symptoms or the change
12 in the underlying cause of Non-24?

13 A. Well, these are obviously the symptoms. This is --
14 these are -- this is sleep data.

15 Q. Now, what kind of data would you expect to be
16 reported if the drug was treating the cause of Non-24?

17 A. I'd expect to see something related to entrainment.
18 And particularly, we would see something about melatonin
19 or cortisol or some hormone that could represent
20 entrainment.

21 Q. Is this data in the label?

22 A. No. No, no.

23 Q. Now, aside from Table 3, did the labels -- do the
24 labels report any other outcomes or results following the
25 treatment of tasimelteon?

1 **A.** No. This is the data in the label.

2 **MR. COBLENTZ:** Now, if we go to DDX-3.10.

3 **BY MR. COBLENTZ:**

4 **Q.** Now, if we go to another part of the Hetlioz label,
5 which is JTX-28, Page 3, the warnings and precautions part
6 of that label, how does this section of the label inform
7 your opinion?

8 **A.** Well, you see that in the warnings and precautions,
9 Number 1 is sleepiness, somnolence. And it says: After
10 taking Hetlioz, patients should limit their activity to
11 preparing for going to bed. They shouldn't go do the
12 laundry, they shouldn't drive to 7-Eleven, they shouldn't
13 text, they should go right to bed.

14 And this is very similar to the warnings and
15 precautions that we would see in the label for a hypnotic
16 agent, whether it be Ambien, Lunesta, Rozerem, these other
17 FDA-approved treatments for insomnia.

18 **Q.** And did you hear Dr. Combs testify that there are
19 portions of the Clinical Trial Study section of Hetlioz
20 label that refer to entrainment?

21 **A.** I did.

22 **Q.** And do you agree with that?

23 **A.** No, no.

24 **Q.** Now, if we go to --

25 **MR. COBLENTZ:** Mr. Brooks, if we can pull up

1 JTX-28.

2 **BY MR. COBLENTZ:**

3 **Q.** We typically go to Page 12, and we call out 14.1, the
4 section here, and look specifically at the third paragraph
5 where it starts Study 2.

6 **A.** Yes.

7 **Q.** Is this one of the portions of the Clinical Study
8 section of the label that Dr. Combs was testifying about?

9 **A.** Yes, it is.

10 **Q.** Now, do you agree with Dr. Combs that this portion of
11 the label instructs a physician that administering
12 tasimelteon to a Non-24 patient will entrain that patient?

13 **A.** No.

14 **Q.** And why don't you agree?

15 **A.** Well, as I said, this is a randomized withdrawal
16 trial. This is where they are taking patients who are
17 already entrained and then they switch them to -- or
18 continued Hetlioz or placebo.

19 And the data that we see is a result in this study,
20 the RESET data that was back there in the label. There's
21 only sleep data that results from this study. No hormonal
22 data, no entrainment data is presented at all.

23 **Q.** And if we go to the last paragraph here of
24 Section 14.1, is this what you were talking about the
25 results of the RESET study?

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1 **A.** Yes, exactly.

2 **Q.** Can you explain this a little bit more?

3 **A.** It says: Treatment with Hetlioz resulted in a
4 significant improvement compared with placebo for both of
5 these study endpoints -- both of these endpoints in
6 study 1 and 2. And it's 2 that we're referring to here.

7 **Q.** Now, we just talked about Dr. Combs. And you heard
8 him testify that the nighttime sleep data and daytime nap
9 data in the Hetlioz label, that that demonstrated
10 entrainment.

11 Did you hear that?

12 **A.** Yes.

13 **Q.** And do you agree with Dr. Combs?

14 **A.** No.

15 **Q.** And why don't you agree?

16 **A.** Maybe you could just repeat the first part? You talk
17 a little too fast.

18 **Q.** I'm sorry.

19 Did you agree with Dr. Combs?

20 **A.** About which specific thing?

21 **Q.** About whether the nighttime sleep data and the
22 daytime naptime data in the Hetlioz label demonstrate
23 entrainment?

24 **A.** No, they don't demonstrate entrainment. They
25 demonstrate clinical improvement of sleep.

1 Q. If we could go back to the slides and go to DDX-3.11.

2 Are there any documents that in your opinion
3 demonstrate that the nighttime sleep and daytime nap data
4 in the Hetlioz label is not representative of entrainment?

5 A. Yes, they are two different documents. And thank you
6 for putting them up there, the clinical study report on
7 the left and the patent on the right.

8 Q. Okay. And let's look at Vanda's clinical study
9 report for the SET study.

10 MR. COBLENTZ: Mr. Brooks, if you could bring
11 up PTX-815.

12 BY MR. COBLENTZ:

13 Q. Do you recognize this document?

14 A. I do.

15 Q. What is it?

16 A. This is the clinical study report for tasimelteon.

17 MR. COBLENTZ: Your Honor, I'd like to move
18 PTX-185 into evidence.

19 MR. KLEIN: I don't believe this was disclosed
20 for Doctor --

21 MR. COBLENTZ: So let me explain here. So what
22 was disclosed -- if we go to the next slide. What was
23 disclosed is JTX-60, which is the full version of the SET
24 study. And we substituted out the less full version. I
25 think the full version was over a thousand pages. So in

1 order to save paper, we actually substituted a version
2 that you guys gave that was much shorter than that.

3 **MR. KLEIN:** No objection.

4 **THE COURT:** All right. It's admitted.

5 (PTX-185 admitted into evidence.)

6 **BY MR. COBLENTZ:**

7 **Q.** So if we look at DDX-3.12 here, what have you called
8 out from this document?

9 **A.** Would have called out are the study objectives. And
10 we're looking at the Primary Objective here -- Objectives
11 and the Secondary Objectives there.

12 **Q.** And for the record, this is on Page 19 of this
13 document.

14 And if we look at the Primary Objectives here, how is
15 entrainment measured in the Primary Objectives?

16 **A.** We've heard a lot about this by -- this melatonin
17 metabolite, aMT6s.

18 **Q.** And was that the endpoint used by Vanda in the study
19 to demonstrate entrainment?

20 **A.** Yes, it was.

21 **Q.** How about Number 2 listed here in the Primary
22 Objectives?

23 **A.** This is a score greater than three on this clinical
24 response scale, which is a composite score of four
25 different endpoints, three of which are explicitly sleep

1 related and the fourth is a clinical global impression,
2 overall impression of how the patient is doing, mostly
3 related, probably, to sleep.

4 **MR. COBLENTZ:** And I've been told by my capable
5 counsel here to clarify that JTX-60, which is here in the
6 slide, we've substituted PTX-815 for that because it is a
7 shorter version of that.

8 So I just wanted to clarify that for the
9 record. They are the same document, one is just shorter
10 than the other.

11 **THE COURT:** I thought you already clarified
12 that. Am I missing something?

13 **MR. KLEIN:** I don't think you are, Your Honor.
14 There's no objection.

15 **MR. COBLENTZ:** Okay.

16 **THE COURT:** I got that, but --

17 **MR. COBLENTZ:** I just wanted to clarify for the
18 purposes of the slide, we meant to -- there's an error in
19 the slide. So I apologize for that. It says JTX-60
20 there; we're actually referring to, for the record,
21 PTX-815.

22 **THE COURT:** I gotcha.

23 **MR. COBLENTZ:** So that's the reason I'm
24 clarifying.

25 **THE COURT:** All right. We're good.

1 **MR. COBLENTZ:** I apologize.

2 **BY MR. COBLENTZ:**

3 **Q.** So if we go back to the clinical study report here
4 and we look at the secondary objectives, we see LQ-nTST
5 and UQ-dTSD.

6 Can you explain those?

7 **A.** Yes, we've been talking about them for the last day
8 or so. These are sleep endpoints, and the T here is time.
9 Total sleep time is TST. And the lowest quartile means
10 the worst 25 percent total sleep time.

11 And TSD is total sleep during the day, and this is
12 the upper quartile or the most naptime during the day.
13 These are obviously sleep endpoints.

14 **Q.** Now, if we look at the second -- or the bullet point
15 that's in the Secondary Objectives here, did Vanda measure
16 urinary cortisol?

17 **A.** Yes. Right there you see it. I will hold this
18 steady, and you can see this is a measure of entrainment.

19 **Q.** Now, how do these endpoints relate to your
20 infringement analysis?

21 **A.** Well, it's clear that the entrainment endpoints are
22 marked as such, entrainment. Whereas the other end point
23 that doesn't say "entrainment" next to them anywhere is
24 sleep. Sleep in 8.1.2 and 8.2 -- 1 and 2. All the green
25 ones are sleep endpoints. You don't see them saying

1 anywhere that those are entrainment endpoints, whereas the
2 other ones, they're clearly marked as entrainment
3 endpoints.

4 **Q.** Now, I would like to go to the RE604 patent, and if
5 we could go to DDX-3.13.

6 And the RE604 patent, which is JTX-1, what are we
7 looking at here on DDX-3.13?

8 **A.** Well, this is data from the patent, first of all.
9 We're switching from the label to the patent. And we see
10 these two tables from the patent.

11 **Q.** Is this Table 1A and Table 1B from the RE604 patent?

12 **A.** Yes, it is.

13 **Q.** And is this the data from Vanda's SET study?

14 **A.** Yes, it is.

15 **Q.** At a high level, what type of data are in Table 1A?

16 **A.** These are the -- as you can see it up here, these are
17 the primary endpoints in 1A, secondary endpoints in 1B.

18 **Q.** What does Table 1A tell us about entrainment?

19 **A.** The patent says that some patients given tasimelteon
20 will entrain. And we can see, in fact, 20.0 percent
21 entraining, whereas less entrained with placebo,
22 2.6 percent.

23 **Q.** How is that measured?

24 **A.** This is through the -- that same melatonin
25 metabolite, aMT6.

1 Q. And this aMT6 data levels, that was not in the drug
2 label?

3 A. No, no. There's nothing about that in the label.

4 Q. Now, in Table 1B, what data have you highlighted
5 here?

6 A. I've highlighted two different things yellow and
7 green. You can see that here in 1B, entrainment is
8 measured with cortisol. And 17.5 percent of people
9 entrained using cortisol, 2.6, again, percent entrained
10 with placebo.

11 On the other hand, there is the sleep data. And our
12 friends, the LQ and the UQ here, and you can see that
13 31.6 percent of those -- of people had improvements in
14 their sleep measures when using these metrics.

15 Q. Now, comparing the LQTST and UQTST data to the
16 entrainment data, why is that significant?

17 A. Well, we can see some people do entrain with
18 tasimelteon. Seventeen to 20 percent using these metrics.
19 But a substantially larger percentage of people entrain --
20 entrain, improve their sleep with tasimelteon.

21 So a much larger percentage of people improve their
22 sleep with tasimelteon than entraining to tasimelteon.

23 Q. And why are there roughly double the number of
24 patients that experience the symptomatic sleep treatment
25 as compared to patients that experience entrainment?

1 **A.** Because this medication, tasimelteon, is -- acts as a
2 sedative. It's helping people sleep, and they fall asleep
3 faster and, therefore, they nap less during the day. I
4 mean, it's a melatonin agonist. Everybody knows that
5 melatonin works as a sedative.

6 **Q.** Now, I'd like to go to DDX-3.15, and I'd like to turn
7 to your opinions on the limitation where the patient
8 awakens at or near a target wake time following that daily
9 sleep period of approximately seven-to-nine hours.

10 **MR. COBLENTZ:** If we can go to DTX-3.16.

11 Let me back up. Let me go back to 3.15.

12 **BY MR. COBLENTZ:**

13 **Q.** What is your opinion on this limitation?

14 **A.** It's my opinion that the defendants do not induce
15 infringement of this limitation of the patent because they
16 do not encourage, recommend, require, or promote the use
17 of the defendants' products as a method in which the
18 patient -- I will use my pointer here -- in which the
19 patient awakens at or near a target wake time following a
20 daily sleep period of approximately seven-to-nine hours.

21 **MR. COBLENTZ:** Now, if we go to DDX-3.16.

22 **BY MR. COBLENTZ:**

23 **Q.** Now, did you hear Dr. Combs testify to his definition
24 of awakens at or near a target time following a daily
25 sleep period of seven-to-nine hours?

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1 **A.** I did.

2 **Q.** Do you agree with it?

3 **A.** No, we have different definitions of this.

4 **Q.** And why do you disagree?

5 **A.** Well, my definition in brief -- I will just synopsise
6 this -- if the patient falls asleep at or near a target
7 bedtime and stays mostly asleep for an approximately
8 seven-to-nine-hour period, stays mostly asleep for
9 seven-to-nine hours, and then wakes up at the end of that
10 approximately seven-to-nine period -- hour period,
11 Dr. Combs refers to a sleep window of approximately
12 seven-to-nine hours during which an individual will
13 consolidate their sleeping, experiencing increased
14 sleepiness within that period. Not sleep increased,
15 sleepiness and wakefulness outside that window.

16 **MR. COBLENTZ:** If we go to DDX-3.17.

17 **BY MR. COBLENTZ:**

18 **Q.** Dr. Combs -- is increased sleepiness within that
19 period that's in Dr. Combs' definition, is that in Claim 1
20 of the RE604 patent?

21 **A.** No. Claim 1 talks about sleep. He talks about
22 sleepiness.

23 **MR. COBLENTZ:** Mr. Brooks, I'd like to pull up
24 JTX-13.

25

1 **BY MR. COBLENTZ:**

2 **Q.** Dr. Winkelman, is this the prosecution history for
3 the RE604 patent?

4 **A.** Yes, it is.

5 **Q.** And did you consider the prosecution history of RE604
6 for your opinions in this case?

7 **A.** I did.

8 **MR. COBLENTZ:** And I'd like to move JTX-13 into
9 evidence.

10 **MR. KLEIN:** No objection.

11 **THE COURT:** All right. It's admitted.

12 (JTX-13 admitted into evidence.)

13 **MR. COBLENTZ:** And for the purposes of the
14 binder, Your Honor, we did not put the thousands of pages
15 that's in here. We just put the declaration just to save
16 some trees, so I just wanted that to be clear.

17 **THE COURT:** Thank you.

18 **BY MR. COBLENTZ:**

19 **Q.** If we go back to the slides and we go to DDX-3.18, is
20 this Dr. Polymeropoulos' declaration from the reissue '604
21 patent prosecution history, and is it consistent with your
22 opinion?

23 **A.** That's correct.

24 **Q.** And how is it consistent with your opinion?

25 **A.** Dr. Polymeropoulos, if we can look at this

1 highlighted section here, says: Treatment of Non-24
2 requires more than just promoting sleep or sleepiness. It
3 requires allowing a patient to fall asleep at
4 approximately his or her bedtime, target bedtime, until
5 awakened at a target wake time following
6 seven-to-nine-hour period of sleep.

7 **Q.** Dr. Winkelman, let's turn to the drug labels.

8 Do defendants' labels mention anywhere a daily sleep
9 period of approximately seven-to-nine hours?

10 **A.** No, nowhere in the label.

11 **Q.** And if we go to DDX- 3.19.

12 Again, we're looking at the Hetlioz label, which is
13 JTX-28 at the Clinical Study section.

14 How much sleep were patients getting before
15 treatment?

16 **A.** So at baseline before any treatment in the SET
17 studies, they were getting 195 minutes of nighttime sleep,
18 so three hours and 15 minutes of sleep.

19 **Q.** And was that on their 25 percent most symptomatic
20 nights?

21 **A.** Yes, I apologize. On the most -- on the 25 percent
22 worst nights.

23 **Q.** And if we look down at Table 3 in the Clinical Study
24 section of the Hetlioz label, did treatment with Hetlioz
25 change the patient's sleep?

1 **A.** It did. It gave them 50 minutes more sleep. So if
2 we add 50 minutes to 195 minutes that they started out
3 with, we end up with 245 minutes; four hours and five
4 minutes of sleep.

5 **Q.** Why is this significant?

6 **A.** Well, it's certainly not seven-to-nine hours' sleep.

7 **Q.** Now, is their information in the Clinical Study
8 section of the label about how long patients should set
9 aside for sleep at night?

10 **A.** No, nothing in the label about that.

11 **Q.** How about consolidating a patient's sleep into one
12 seven-to-nine-hour period? Is there anything in the label
13 about that?

14 **A.** No, no.

15 **Q.** Is there anything in the label that discusses a
16 patient taking tasimelteon would cause them to wake up at
17 a target wake time?

18 **A.** Not aware of that.

19 **Q.** Is there any information in the label about a hope
20 that these patients will get seven-to-nine hours of sleep?

21 **A.** Nope.

22 **Q.** Is there anything in the Hetlioz label about the goal
23 for treating Non-24 patients with tasimelteon is getting
24 seven-to-nine hours of sleep?

25 **A.** No.

1 Q. If we go to DDX-3.20, I want to turn to the -- your
2 opinions on the DDI patents, the ones that have a CYP
3 patent claim.

4 A. Okay.

5 Q. Have you seen any evidence that a single patient was
6 being treated with a strong CYP1A2 inhibitor or a CYP3A4
7 inducer presented to a physician with a diagnosis of
8 Non-24?

9 A. No.

10 Q. Have you ever seen any evidence that a single patient
11 has had treatment with a strong CYP1A2 inhibitor or a
12 CYP3A4 inducer discontinued in order to treat Non-24 with
13 tasimelteon?

14 A. No, never.

15 Q. Now, if such a patient were to present in a clinic
16 with Non-24, would the defendants' labels instruct
17 physicians to discontinue administration of either the
18 CYP1A2 inhibitor or the CYP3A4 inducer and begin treatment
19 with tasimelteon?

20 A. No.

21 Q. I'd like to go to DDX-3.21.

22 Dr. Winkelman, regarding the asserted claims with the
23 CYP limitations, which is the '829 and the '910 patent,
24 what is your opinion on whether defendants' labels would
25 induce infringement of these limitations?

1 **A.** It's my opinion that they would not induce
2 infringement of the CYP portion of the patent. They do
3 not encourage, recommend, require, or promote these
4 behaviors which are explicitly mentioned and described in
5 the patent in this particular order:

6 Determine whether a patient is being treated with
7 inducer or inhibitor;

8 Two, discontinue treatment with the inhibitor or
9 inducer; and

10 Three, treat the patient with tasimelteon.

11 **Q.** Now, I'd like to go to DDX-3.21.

12 What do the drug labels instruct a prescriber to do?

13 **A.** To avoid the use of Hetlioz in combination with these
14 inducers or inhibitors.

15 **Q.** Now, for the record, you are looking at the Hetlioz
16 label, the drug interactions section of the label; is that
17 correct?

18 **A.** That's correct. Right there, 7. It's always the
19 section of interactions.

20 **Q.** Now, why is it telling prescribers don't coadminister
21 enough?

22 **A.** Why is --

23 **Q.** Why is -- why is it telling -- why isn't -- let me
24 enunciate correctly.

25 Why isn't telling prescribers "don't coadminister

1 these drugs" enough to induce infringement?

2 **A.** Because it suggests that there are a variety of ways
3 to avoid this combination.

4 **Q.** What do defendants' labels tell a prescriber about
5 discontinuing a CYP1A2 inhibitor or a CYP3A4 inducer prior
6 to treating with tasimelteon?

7 **A.** The labels say nothing of the kind.

8 **Q.** Would this be a patient-specific decision?

9 **A.** I certainly would hope so.

10 These are important decisions that we make about
11 patients, and we make them based upon the patient and the
12 risks and benefits for that patient using this medication
13 or that medication, and it is absolutely always
14 patient-specific.

15 **Q.** Now, if we go to DDX-3.23.

16 I want to look at the three CYP1A2 inhibitors and the
17 CYP3A4 inducers that are mentioned in the patent claims.

18 What is fluvoxamine?

19 **A.** Fluvoxamine is an SSRI, selective serotonin reuptake
20 inhibitor. It is FDA-approved for the treatment of OCD,
21 oftentimes used in severe OCD. Used also for major
22 depressive disorder.

23 **Q.** What is verapamil?

24 **A.** Verapamil is a calcium channel antagonist. It's used
25 to treat hypertension, a variety of heart arrhythmias,

1 coronary artery disease. A variety of cardiac issues.

2 Q. What is ciprofloxacin?

3 A. Ciprofloxacin is an antibiotic, and it treats a
4 variety of bacterial infections.

5 Q. And I'm going to refer to that as Cipro going forward
6 so I don't mess that up again.

7 What is rifampicin?

8 A. Rifampicin or rifampin is also an antibiotic. This
9 is a medication that's used to treat TB. It's used to
10 treat leprosy; you can't treat leprosy without rifampin.
11 And it's used to treat Legionnaires' disease.

12 These are serious and disfiguring bacterial diseases.

13 Q. Now, if we go to DDX-3.24, what is your opinion about
14 whether a prescriber would discontinue fluvoxamine and
15 then treat a patient with tasimelteon?

16 A. I don't think most providers would do that, honestly.
17 OCD can be hard to treat. If they are effectively treated
18 with Luvox, fluvoxamine, for their OCD, it would be super
19 unusual to stop that. And honestly, what most people
20 would do is just use another medication to treat the
21 Non-24. You don't want to mess with someone who has OCD
22 that's well treated.

23 MR. COBLENTZ: Mr. Brooks, if we could please
24 pull up DTX-132.

25

1 **BY MR. COBLENTZ:**

2 **Q.** Is this the label for Luvox or fluvoxamine?

3 **A.** That's correct.

4 **Q.** I believe this has already been entered into
5 evidence.

6 If we could go back to Slide 26.

7 And how did the precautions in the --

8 **A.** The one before?

9 **Q.** Oh, I'm sorry 25.

10 How do the precautions in the fluvoxamine label at
11 DTX-132.11 inform your analysis?

12 **A.** Well, stopping the Luvox would not just make their
13 OCD come back, probably. But when you stop an SSRI, many
14 people have very uncomfortable side effects from doing
15 that. And you see the list of them. I am not going to go
16 through them, but some of these are transient, some of
17 them are not so transient. It's a decision you want to
18 make very carefully.

19 **Q.** Let's go to DDX-3.26.

20 What is your opinion about whether a prescriber would
21 discontinue verapamil and then treat a patient with
22 tasimelteon?

23 **A.** I don't think so. Again, they're being treated with
24 verapamil for their hypertension, for their coronary
25 artery disease, arrhythmia, a variety of significant

1 cardiac diseases. I think that, instead, patients --
2 prescribers would not start Hetlioz and would use an
3 alternative medication to address the Non-24 rather than
4 stopping the verapamil.

5 **Q.** Now, if we go to DDX-3.27.

6 What is your opinion about whether a prescriber would
7 discontinue Cipro and rifampicin, then treat a patient
8 with tasimelteon?

9 **A.** Well, Cipro, really, or rifampicin -- they probably
10 wouldn't be taking both. But I think that they would be
11 extremely cautious in making this decision, particularly
12 with rifampin.

13 The rifampin treatment for these bacterial diseases
14 is really essential. And these are serious illnesses.
15 And I really don't think that they would stop rifampin so
16 that they could start Hetlioz. They would use some other
17 approach to addressing the patient's Non-24 symptoms,
18 whether it be melatonin or some other agent.

19 **MR. COBLENTZ:** Mr. Brooks, if we could please
20 bring up DTX-128.

21 **BY MR. COBLENTZ:**

22 **Q.** Now, Dr. Winkelman, is this the label for Cipro?

23 **A.** That's correct.

24 **MR. COBLENTZ:** And Mr. Brooks, if we could
25 bring up DTX-129.

1 **BY MR. COBLENTZ:**

2 **Q.** Dr. Winkelman, is this the label for rifampicin?

3 **A.** Correct.

4 **Q.** And did you consider these two labels as part of your
5 opinion?

6 **A.** I did.

7 **MR. COBLENTZ:** I think DTX-128 has already been
8 moved in.

9 But I would like to move in DTX-129 into
10 evidence.

11 **MR. KLEIN:** No objection.

12 **THE COURT:** All right. It's admitted.

13 (DTX-129 admitted into evidence.)

14 **MR. COBLENTZ:** If we could go back to the
15 slides, and go to DDX-3.28.

16 **BY MR. COBLENTZ:**

17 **Q.** Now, if we look at the label for Cipro at DTX-128.42
18 and the label for rifampin at DTX-129.9, how does this
19 inform your analysis?

20 **A.** Well, it says skipping doses or not completing the
21 full course, i.e., distinct treatment, can cause two bad
22 things.

23 One, they are not going to get fully treated,
24 obviously. The treatment, just to note, for TB with
25 rifampin is four months in duration; for leprosy is two

1 years in duration. So they are not going to get fully
2 treated if you discontinue treatment. And even worse, I
3 don't know, maybe not even worse, but in addition, they
4 could develop bacterial resistance, which is really -- you
5 want to avoid.

6 **Q.** Dr. Winkelman, were you here when Dr. Combs testified
7 that a prescriber could wait until the patient has
8 completed the treatment course of these drugs before
9 initiating tasimelteon treatment?

10 **A.** Yes, I was.

11 **Q.** In your opinion, does this fall within the patent
12 claims?

13 **A.** No.

14 **Q.** And why not?

15 **A.** The patent claims say discontinue treatment. They
16 don't say continue the treatment and then do something.

17 **MR. KLEIN:** Objection, Your Honor. I don't
18 believe this testimony is in Dr. Winkelman's report.

19 **MR. COBLENTZ:** We'll move on.

20 **MR. KLEIN:** We're moving to strike.

21 **MR. COBLENTZ:** Okay. That's fine.

22 **THE COURT:** Okay.

23 **MR. COBLENTZ:** We'll pass the witness.

24 **THE COURT:** Struck.

25 And go ahead, Mr. Klein.

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1 **MR. KLEIN:** Your Honor, may we approach?

2 **THE COURT:** Yes, please.

3 CROSS-EXAMINATION

4 **BY MR. KLEIN:**

5 **Q.** Good afternoon, Dr. Winkelman.

6 **A.** Good afternoon.

7 **Q.** I'd like to pick up with a question that the Court
8 had asked you.

9 So the condition of Non-24 Hour Sleep-Wake Disorder
10 is defined by "lack of entrainment," correct?

11 **A.** Yes.

12 **Q.** And if you have untreated Non-24, the circadian
13 rhythm isn't entrained, correct?

14 **A.** That's correct.

15 **Q.** And lack of entrainment is the only known cause of
16 Non-24.

17 **A.** I think that's probably true.

18 **Q.** And while it doesn't work in everybody, in some
19 individuals, tasimelteon can entrain the circadian rhythm,
20 correct?

21 **A.** That is true from the data in the patent. That is
22 clearly not evident in the label.

23 **Q.** But my question was, in some patients, individual --
24 in some individuals, tasimelteon can entrain their
25 circadian rhythms; is that correct?

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1 **A.** Well, it depends where you are getting your
2 information from.

3 **Q.** If a patient takes tasimelteon for Non-24, according
4 to the dosing and administration regimen set forth in the
5 tasimelteon label, some patients will entrain, correct?

6 **A.** Again, if you're a prescriber like me, and you're
7 reading the label, that would not be evident.

8 **Q.** That wasn't my question.

9 **A.** Well, the information has to come from someplace that
10 somebody gets. So I'm not sure how to answer your
11 question, honestly.

12 **Q.** I will ask the question again, and then maybe we'll
13 turn to your deposition.

14 If a patient takes tasimelteon for Non-24, according
15 to the dosing and administration regimen set forth in the
16 tasimelteon label, some of those patients will entrain,
17 correct?

18 **A.** I don't know. I think we went through this a few
19 times.

20 **Q.** That's fine. Do you have your white binder up there?

21 **A.** I do.

22 **Q.** Can you turn to the first tab, please.

23 **A.** Yes.

24 **Q.** And when you get there, can you confirm that you
25 recognize that that's the transcript of the deposition

1 that you gave in this case?

2 **A.** Yes, I think so.

3 **MR. KLEIN:** And, Mr. Weir, can you pull up
4 Page 188, Lines 17 through 25.

5 **BY MR. KLEIN:**

6 **Q.** And, Dr. Winkelman, I'm referring you to Line 17
7 through 25 on Page 188.

8 The question was: So given all that, you would agree
9 that some patients will entrain on tasimelteon if treated
10 for Non-24, according to the dosing and administration
11 regimen set forth in the tasimelteon label, correct?

12 "I would agree" was your answer, correct?

13 **A.** That was my answer.

14 **Q.** So if tasimelteon is administered once daily at the
15 same time every night before bedtime in a dose of
16 20 milligrams, some of those patients will be entrained,
17 correct?

18 **A.** The context from this, from the deposition, if we
19 look at the context is we're talking about FDA, the data,
20 data that was presented to the FDA, data that was from the
21 full SET trial.

22 **Q.** The question that I just read to you from your
23 deposition was referring to the dosing and administration
24 regimen set forth in the tasimelteon label, correct?

25 **A.** Yes.

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1 Q. And you would agree --

2 A. The first -- I'm sorry to interrupt.

3 Q. And you would agree the dosing and administration
4 regimen is set forth in the tasimelteon label, correct?

5 A. It certainly is. The first part of your question was
6 "so given all that." And so I think we need to understand
7 what's given and what's not given before somebody who
8 knows something or not. So what was given there before
9 was the FDA information.

10 Q. My question is --

11 MR. COBLENTZ: Your Honor, for completeness
12 sake, can they read the question before that to give
13 context to that -- to what -- to give context to "so given
14 all that"?

15 THE COURT: You can do that on redirect.

16 MR. COBLENTZ: Okay.

17 THE COURT: Well, you know, I mean, you can
18 also object if it's not an inconsistent statement.
19 There's enough here to explore it. You can pick it up on
20 direct. I get the point.

21 BY MR. KLEIN:

22 Q. So, Dr. Winkelman, my question is: What will happen
23 if somebody takes the pill according to the dosing regimen
24 specified in the label?

25 A. I think we know from what the patent says and from

1 the data that I presented there, that some patients will
2 entrain.

3 Q. So let's switch topics somewhat.

4 Non-24 is a cyclical disorder, correct?

5 A. Its symptoms are cyclical disorder. A sleep
6 disturbance is a cyclical disorder. It is not a cyclical
7 disorder, really.

8 Q. Patients with Non-24 will sleep in line with the
9 light/dark cycle at some times, but not at others in a
10 cyclical way, correct?

11 A. That's correct.

12 Q. The cyclical nature of Non-24 is a result of
13 patients' circadian rhythms not being entrained, correct?

14 A. That is correct.

15 Q. When a patient with Non-24 is out of phase, they
16 sleep less at night and more during the day, correct?

17 A. Than when they're in phase, you mean?

18 Q. Yes.

19 A. Yes.

20 Q. And decreased sleep at night and increased sleep
21 during the day are caused by lack of entrainment in Non-24
22 patients, correct?

23 A. That is correct.

24 Q. And clinicians who practice sleep medicine would know
25 that decreased sleep at night and increased sleep during

1 the day for Non-24 patients is caused by their lack of
2 entrainment, correct?

3 **A.** That's one of the causes. They may have other
4 causes. They may have additional causes of insomnia.
5 But, certainly, that's one of causes, yes.

6 **Q.** And a clinician would know that, correct?

7 **A.** And a clinician would know that.

8 **Q.** So let's talk about how Non-24 is treated.

9 **A.** Yeah.

10 **Q.** Ideally, for a Non-24 patient with no light
11 perception, treatment would entrain them the way sunlight
12 entrains a healthy sighted person, so their circadian
13 rhythm and sleep/wake cycle are on 24-hour schedule?

14 **A.** What would entrain them?

15 **Q.** Sunlight. I'll repeat the question.

16 Ideally, for a Non-24-hour patient with no light
17 perception, treatment would entrain them the way sunlight
18 entrains a healthy sighted person, so that their circadian
19 rhythm and sleep/wake cycle are on a 24-hour rhythm?

20 **A.** Yes.

21 **Q.** Now, if you gave Ambien to a patient with Non-24 at
22 night, and a stimulant to that same patient in the
23 daytime, you wouldn't be addressing the cause of their
24 Non-24, correct?

25 **A.** That's correct.

1 Q. You would only be treating their symptoms, correct?

2 A. You'd be treating what they came to you complaining
3 of, which is sleep problems.

4 Q. You would be treating their symptoms, correct?

5 A. You would be treating their symptoms.

6 Q. You've heard the term "soporific," correct?

7 That's a drug that induces sleep?

8 A. Yes.

9 Q. Tasimelteon actually has some soporific properties,
10 correct?

11 A. Yes.

12 Q. You're not supposed to drive after you take it?

13 A. Right.

14 Q. But Tasimelteon is not a purely soporific drug,
15 correct?

16 A. It has a variety of mechanisms of action.

17 Q. And it has mechanisms of action that are not purely
18 soporific in nature, correct?

19 A. That's correct.

20 Q. Which is to say that it has properties that won't act
21 merely to -- withdrawn.

22 It has properties that are not going to sedate the
23 patient, correct?

24 A. It has sedative properties and it has non-sedative
25 properties.

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1 Q. And those non-sedative properties are regulating the
2 circadian rhythm, correct?

3 A. It can contribute to that.

4 Q. And by "contribute to that," you mean that it can
5 regulate the circadian rhythm, correct?

6 A. To some extent.

7 Q. You testified on your direct that the label discloses
8 treating sleep disturbances in Non-24 patients, correct?

9 A. Sorry. Could you repeat it?

10 Q. In your direct -- I'm sorry?

11 A. You just talk fast.

12 Q. I will try to slow down for everyone's benefit.

13 You testified on your direct that the Hetlioz label
14 discloses treating sleep disturbances, correct?

15 A. Yes.

16 Q. So let's look at the Hetlioz label, which is in your
17 black binder, because I didn't put it in your white
18 binder, which is JTX-028.

19 A. This?

20 Q. Yes. The one Mr. Coblentz gave you.

21 A. Okay.

22 MR. KLEIN: Your Honor, is it okay to proceed?

23 THE COURT: Oh, yes, please.

24 BY MR. KLEIN:

25 Q. Okay. So you're aware that Hetlioz is also approved

1 for treatment of Smith-Magenis syndrome, correct?

2 **A.** I am aware of that, yes.

3 **MR. KLEIN:** Mr. Weir, can you please pull up in
4 JTX-28, Page 1, the section under Indications and Usage,
5 all the way to the bottom, before you get to Dosage and
6 Administration, please.

7 Under Indications and Usage at the top, yep.
8 Little bit further down. That's fine. That's fine.

9 Yep. Perfect. Thank you.

10 **BY MR. KLEIN:**

11 **Q.** And what is Smith-Magenis syndrome?

12 **A.** I really know very little about it, except that it is
13 a rare genetic disorder which produces, among other
14 things, sleep disturbance.

15 **Q.** So you understand that it's a genetic disorder,
16 correct?

17 **A.** That much I know.

18 **Q.** And Non-24 is not a genetic disorder, correct?

19 **A.** Not as far as we know.

20 **Q.** And when the Hetlioz label is referring to the
21 indication of tasimelteon for the treatment of
22 Smith-Magenis Syndrome, it refers to nighttime sleep
23 disturbances in Smith-Magenis syndrome, correct?

24 **A.** That's what it says, yes.

25 **Q.** And that would be referring to treatment of the

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1 symptoms of Smith-Magenis syndrome, correct?

2 **A.** I think so.

3 **Q.** In contrast, when the same label is referring to the
4 indication of Hetlioz as related to Non-24, it says Non-24
5 Sleep-Wake Disorder, correct?

6 **A.** It does say that.

7 **Q.** And you've already agreed that Non-24 Sleep-Wake
8 Disorder is defined by lack of entrainment, correct?

9 **A.** Correct.

10 **Q.** And with respect to in defendants' tasimelteon
11 labels, nowhere in there does it refer to sleep
12 disturbances, correct?

13 **A.** It talks about very poor sleep.

14 **Q.** Does it use the word "sleep disturbances"?

15 **A.** I don't -- it may not use the word "sleep
16 disturbance." It talks about people getting three hours
17 and five minutes of sleep. That's a sleep disturbance.

18 **MR. KLEIN:** Are we able to pull up DDX-3.19?

19 Let me just switch controls. You can take that down.

20 **BY MR. KLEIN:**

21 **Q.** This is a slide you prepared, Dr. Winkelman?

22 **A.** Yes.

23 **Q.** And when we see on this slide that patients in the
24 chart -- in the Table 3 -- "nighttime sleep time on
25 25 percent most symptomatic nights."

1 Do you see that?

2 A. Yes.

3 Q. That's referring to the amount of sleep patients got
4 when they were most out of phase in their circadian
5 rhythm, correct?

6 A. Well, in this part, it is how much additional sleep
7 they got, yes.

8 Q. But you understand that the 25 percent of most
9 symptomatic nights is referring to the 25 percent of the
10 patient's nights when they were the most out of phase?

11 A. We don't know that. We know that they were their
12 25 percent worst nights. We don't know whether they were
13 out of phase at that point or in phase at that point.

14 Q. Does anything in the label tell you that patients got
15 less than seven hours of sleep during their 25 percent of
16 best nights of sleep?

17 A. Their best nights of sleep?

18 Q. Yeah. The opposite of the 25 percent --

19 A. No, I haven't seen any data on that.

20 Q. Okay. So let's talk about melatonin acrophase.

21 Melatonin acrophase is the moment in a person's cycle
22 when their melatonin levels are at their highest level,
23 correct?

24 A. At the peak, yes.

25 Q. At the peak.

1 The melatonin cycle plays a role in circadian rhythm
2 disorders, including Non-24, correct?

3 **A.** Yes.

4 **Q.** Another rhythm that cycles through the day is the
5 cortisol rhythm?

6 **A.** Correct.

7 **Q.** Cortisol is another hormone?

8 **A.** It is.

9 **Q.** It has an acrophase as well?

10 **A.** It does.

11 **Q.** Would you agree that most clinicians who practice
12 sleep medicine would understand the concept of melatonin
13 acrophase as it relates to circadian rhythm sleep
14 disorders?

15 **A.** Probably, yes.

16 **Q.** And people who treat Non-24, would you expect them to
17 be familiar with the concept of melatonin acrophase or
18 cortisol acrophase as it relates to Non-24 Sleep-Wake
19 Disorder?

20 **A.** Well, people who treat Non-24 are not necessarily
21 sleep physicians. It's a drug that's marketed widely to
22 physicians across the United States. So they may or may
23 not. But sleep physicians would definitely know that.

24 **Q.** Okay.

25 **MR. KLEIN:** So, Mr. Weir, can you please pull

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1 up Page 60 of Dr. Winkelman's deposition transcript. The
2 lines are --

3 **THE WITNESS:** Do you want me to look at this
4 here?

5 **MR. KLEIN:** Yes, please. Page 60 of -- it
6 carries over onto Page 61. But it's page --

7 **THE WITNESS:** Hold on a second.

8 **MR. KLEIN:** Sure.

9 And, Mr. Weir, we're going to focus on Page 60,
10 Line 22, through Page 61, Line 3.

11 **BY MR. KLEIN:**

12 **Q.** The question you were asked was:

13 **"Q.** So people who treat Non-24, would you expect them to
14 be familiar with the concept of melatonin acrophase or
15 cortisol acrophase as it relates to Non-24?"

16 The answer:

17 **"A.** I think so, yes."

18 That was your testimony, correct?

19 **A.** That is my testimony.

20 Again, I'm sorry to do this, but just looking at the
21 context here and all of the previous context was
22 clinicians who practice sleep medicine, and quite a
23 very -- a bit of variability in sleep medicine doctors.
24 Pulmonologist, I said, not so much. Not to diss on them.

25 But it's -- I think we can't generalize this to all

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1 sleep doctors, or certainly all doctors. But sleep
2 medicine doctors, I would agree, yes.

3 Q. Sleep medicine doctors, you would agree?

4 A. Sleep specialists who see and treat Non-24 would
5 understand acrophase, melatonin acrophase, circadian
6 acrophase.

7 Q. And they would understand it to be in the context of
8 Non-24, correct?

9 A. In the label?

10 Q. I'll ask the question differently.

11 Those -- that population of physicians that you just
12 specified, those people would understand that melatonin
13 acrophase would be an indicator of the -- a patient's
14 entrainment or lack of entrainment, correct?

15 A. Yes.

16 Q. And you can tell that someone with Non-24 is
17 entrained by looking at whether their melatonin acrophase
18 drifts or delays day to day, as opposed to occurring at
19 the same time every day, correct?

20 A. Yes, it can.

21 Q. And, again, do you think most sleep medicine
22 clinicians who treat patients with Non-24 would understand
23 that?

24 A. I think so, yes.

25 Q. So, Dr. Winkelman, let's turn to, now, in the white

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1 binder, JTX-030, please.

2 **A.** Got it.

3 **Q.** And if you could turn to Page 9 of 10.

4 **MR. KLEIN:** Mr. Weir, can you go to Page 9 of
5 10 of JTX-030, please.

6 And can you blow up the first paragraph,
7 please. Thank you.

8 **BY MR. KLEIN:**

9 **Q.** Dr. Winkelman, do you see the sentence that says:
10 Patients in whom the calculated time of peak melatonin
11 level (melatonin acrophase) occurred at approximately the
12 same time of day in contrast to the expected daily delay?

13 **A.** I'm just trying to find it here. Sorry. Give me a
14 second.

15 **Q.** That's fine.

16 **A.** Patients in -- yes.

17 **Q.** Yep. In contrast to the expected daily delay?

18 **MR. KLEIN:** Mr. Weir, could you highlight that?
19 All the way -- okay.

20 **THE WITNESS:** Yes. I'm certainly familiar with
21 that.

22 **BY MR. KLEIN:**

23 **Q.** Okay. This language is referring to entrainment,
24 correct?

25 **A.** Yes.

1 Q. And a clinician who treats sleep disorders or Non-24
2 would understand that, right?

3 A. I think so.

4 Q. So let's switch topics again a little bit.

5 You understand the difference between exogenous
6 melatonin and endogenous melatonin, correct?

7 A. I do.

8 Q. Endogenous melatonin is the hormone made within our
9 body, and exogenous melatonin is the stuff Mr. Groombridge
10 had shown in his opening presentation, correct?

11 A. Well, I didn't see that performance, but I believe
12 you.

13 Q. If a person takes exogenous melatonin, a pill or
14 capsule, it can throw off the measurement of their
15 melatonin acrophase, correct?

16 A. It could, yes.

17 Q. And that's because it would be hard to get a read of
18 the body's endogenous melatonin levels when there was also
19 exogenous melatonin in the bloodstream, correct?

20 A. Yes, you would see the metabolite from the exogenous.

21 Q. And the endogenous, correct?

22 A. As well as the endogenous.

23 Q. So let's talk about someone who isn't taking
24 exogenous melatonin.

25 If a patient is not taking exogenous melatonin and

1 their calculated time, take melatonin, or melatonin
2 acrophase occurred at approximately the same time of day,
3 you would know that person was entrained, correct?

4 **A.** You would probably know that, yes.

5 **Q.** And most sleep medicine clinicians who treat Non-24
6 would understand that if a patient is not taking exogenous
7 melatonin and their calculated time of peak melatonin or
8 melatonin acrophase occurred at approximately the same
9 time of day, that that person was entrained, correct?

10 **A.** Probably, yes.

11 **Q.** And would you expect most sleep medicine clinicians
12 to understand that if a patient is not taking exogenous
13 melatonin, that that phenomenon would show they were
14 entrained, correct?

15 **A.** That phenomenon, the stability of their melatonin
16 acrophase?

17 **Q.** Correct.

18 **A.** Yes.

19 **Q.** If a clinician was treating somebody with Non-24 and
20 determined that the patient's calculated time of peak
21 melatonin or melatonin acrophase delayed every day, they
22 would know that that person was not entrained, correct?

23 **A.** That is probably true, yes.

24 **Q.** If that clinician, then, administered some kind of
25 intervention and then measured peak melatonin or melatonin

1 acrophase again and found that it was now occurring at
2 approximately the same time of day every day, they would
3 have concluded that that intervention entrained that
4 patient, correct?

5 **A.** Probably, yes.

6 **Q.** And, again, most sleep medicine clinicians who treat
7 Non-24 would understand that phenomenon, correct?

8 **A.** Yes, I think so.

9 **Q.** So let's look at -- well, if you still have JTX-030
10 in front of you. And if you can go to the first page,
11 actually.

12 **MR. KLEIN:** And, Mr. Weir, can you pull up
13 JTX-030, go to the first page and blow up the box under
14 Dosage Administration, top left, all the way -- yeah.
15 Perfect. Thank you.

16 **BY MR. KLEIN:**

17 **Q.** So we're just going to focus on the dosage and
18 administration to the bottom of that blowup.

19 This language instructs the -- well, withdrawn.

20 You see the language "administer at the same time
21 every night" underneath the box, the chart?

22 **A.** I do.

23 **Q.** And this language instructs prescribers to administer
24 tasimelteon at a fixed clock time every day, correct?

25 **A.** It instructs them to tell the patient to administer

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1 it at same time every night. I mean, the doctor is not at
2 the patient's house.

3 **Q.** The doctor will prescribe -- well, the doctor will
4 instruct the patient to take it at the same time every
5 night, right?

6 **A.** Correct.

7 **Q.** At a fixed clock time, correct?

8 **A.** At the same time every night.

9 **Q.** Yep. And that's what this language is instructing a
10 prescriber to do, correct?

11 **A.** Correct.

12 **Q.** Okay. A clinician would understand the significance
13 of administering tasimelteon at a fixed clock time so that
14 it can act as a circadian cue, correct?

15 **A.** I disagree.

16 **MR. KLEIN:** So let's look at Page 193 of
17 Dr. Winkelman's transcript, Mr. Weir. Page 193, Line 20.

18 **THE WITNESS:** This is back to the black binder?

19 **BY MR. KLEIN:**

20 **Q.** No, you're in the white binder, first tab, Page 193.

21 **A.** Oh. Got it.

22 **Q.** And we're going to look at 193, Line 20 through
23 194 -- Page 194, Line 14.

24 And so the question was:

25 **"Q.** So a clinician would understand the significance of

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1 administering tasimelteon at a fixed clock time so that it
2 acts as a circadian cue, correct?"

3 And you said:

4 "A. They would understand that that was the intention."

5 A. Let me look at the context again. Sometimes this
6 alters .

7 Q. I'm trying to confirm that that was your testimony.

8 A. Oh. It appears that I said that, yes.

9 Q. Okay. A circadian cue is something you would want to
10 happen on a 24-hour schedule if you were trying to entrain
11 someone, correct?

12 A. Yes.

13 Q. Did you read the entirety of the Hetlioz label and
14 the defendants' label in preparing for your testimony
15 today?

16 A. Yes, of course.

17 Q. You agree that all the words on a drug label provide
18 important information that a prescriber should read,
19 correct?

20 A. Yes.

21 Q. And did I hear you say that the drug interaction
22 information in a drug label is always in Section 7 of a
23 drug label, correct?

24 A. I think that's true.

25 Q. And a doctor who regularly prescribes medicine would

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1 know that, correct?

2 **A.** I think so.

3 **Q.** Including sleep medicine physicians, correct?

4 **A.** A sleep medicine doctor is just like every other
5 doctor.

6 **Q.** So can you turn to JTX-030, which, again, is the Teva
7 label. And we're going to look at Section 7.

8 **MR. KLEIN:** Mr. Weir, can you pull up JTX-030,
9 Page 3 of 10. And highlight from Section 7, Drug
10 Interactions, through 7.2. Thank you.

11 **BY MR. KLEIN:**

12 **Q.** All right. And, then, so, Doctor --

13 **THE COURT:** The witness is scratching his back
14 or something.

15 **THE WITNESS:** Sorry. Doing little pushups here
16 just to stretch.

17 **MR. KLEIN:** It's all right.

18 **THE WITNESS:** I can listen and do pushups at
19 the same time.

20 **MR. KLEIN:** That's fine with me.

21 **THE WITNESS:** Sorry.

22 **MR. KLEIN:** It's okay.

23 **BY MR. KLEIN:**

24 **Q.** So can you --

25 **THE COURT:** So the record is clear for the

1 appeals court, you are sitting in your chair doing the
2 pushups.

3 **BY MR. KLEIN:**

4 **Q.** So can you -- I want to focus your attention on
5 Section 7.1, which has the title "Strong CYP1A2
6 Inhibitors, e.g. Fluvoxamine."

7 Do you see that, Dr. Winkelman?

8 **A.** I do.

9 **Q.** And Section 7.1 says: Avoid use of tasimelteon in
10 combination with fluvoxamine or other strong CYP1A2
11 inhibitors because of a potentially large increase in
12 tasimelteon exposure and greater risk of adverse
13 reactions.

14 Do you see that?

15 **A.** Yes.

16 **Q.** This language recommends or instructs clinicians to
17 take one of two courses of action if they have a patient
18 who has Non-24 and is taking fluvoxamine or another CYP1A2
19 inhibitor.

20 Option 1, discontinue the CYP1A2 inhibitor, such as
21 fluvoxamine --

22 (Reporter interruption.)

23 **Q.** Option 1, discontinue the CYP1A2 inhibitor, such as
24 fluvoxamine, and administer tasimelteon; or Option 2,
25 don't administer tasimelteon. Let the patient stay on

1 their CYP1A2 inhibitor medication, such as fluvoxamine.

2 Do you agree that those are the two options
3 contemplated by this language?

4 **A.** Seems reasonable, yes.

5 **Q.** So you agree that that's one -- that -- one of those
6 two options.

7 **A.** Those two, yes.

8 **Q.** Those two.

9 And in your direct examination, you said
10 nevertheless, you don't agree that this label promotes
11 Option 1.

12 Is that your testimony?

13 **A.** Option 1 being discontinue the fluvoxamine?

14 **Q.** Correct.

15 **A.** Yes.

16 **Q.** So it's your testimony that the label language
17 doesn't promote discontinuing fluvoxamine and giving
18 tasimelteon, but that Option 1 is contemplated as one of
19 the two options a prescriber could take reading that
20 language, correct?

21 **A.** Agreed.

22 **Q.** Okay. And so let's look at Section 7.2. It's still
23 on the screen. The title is Strong CYP3A4 Inducers, e.g.,
24 Rifampin.

25 Do you see that?

1 **A.** Yes.

2 **Q.** And this says: Avoid use of tasimelteon in
3 combination with rifampin or other CYP3A4 inducers... And
4 then it goes on.

5 Do you see that?

6 **A.** Yes.

7 **Q.** I'm going to give you the same question.

8 So you would agree that the two options contemplated
9 by this language is either not give the CYP3A4 inducer and
10 give tasimelteon, or keep the patient on the CYP3A4
11 inducer and don't give tasimelteon, correct?

12 **A.** It's the corollary of what we said before, yes.

13 **Q.** And you still don't agree that this language promotes
14 Option 1, correct, giving tasimelteon and not giving
15 rifampin?

16 **A.** No. Doctors just wouldn't do that.

17 **Q.** Okay. And fluvoxamine is used to treat
18 obsessive-compulsive disorder, correct?

19 **A.** Correct.

20 **Q.** If a clinician had another way of treating the
21 patient's obsessive-compulsive disorder, such as with the
22 drug Zoloft, which is not a CYP1A2 inhibitor, then they
23 would be able to practice the language of Section 7.1 by
24 discontinuing fluvoxamine and giving tasimelteon, correct?

25 **A.** That is an option. That's not something a doctor

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1 would do. They are being effectively treated for their
2 OCD, and the doctor says, I want to switch you to this
3 other medicine which may or may not work as well for your
4 OCD as fluvoxamine so that you can take Hetlioz which has
5 a chance of improving your symptoms, definitely no.
6 That's not -- risks and benefits. The risk there is too
7 great compared to the benefit.

8 It's an option; not something they would do.

9 **Q.** Okay. You agree that drugs like fluvoxamine used to
10 treat psychiatric disorders sometimes don't work in
11 patients, correct?

12 **A.** Correct.

13 **Q.** And sometimes a patient needs to try multiple
14 psychiatric medications until they find one that works for
15 them, correct?

16 **A.** Unfortunately, yes.

17 **Q.** Can you go to your black binder, please, the one that
18 Mr. Coblentz gave you, and I want to refer you to DTX-132.

19 **A.** Got it. I'm there.

20 **Q.** If we go to Page 7, DTX-132.

21 **A.** Yes.

22 **Q.** You are there, Dr. Winkelman?

23 **A.** Yes.

24 **Q.** And just -- well, so we have it, this is the label
25 for fluvoxamine that you talked about in your direct

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1 examination, correct?

2 **A.** Yes.

3 **Q.** And you actually talk about this section that we're
4 looking at here on Page 7, correct?

5 **A.** The following symptoms, blah, blah, blah...

6 I'm trying to find the exact part that we put up
7 there.

8 **Q.** Sure.

9 **A.** I think I talked about a part where we discontinued.

10 **Q.** Exactly, right.

11 **A.** And I'm trying to find that on this page.

12 **Q.** Well, I can -- I don't need you to find it. I want
13 to focus your attention to the second-to-last paragraph.

14 **A.** Okay.

15 **Q.** And the first sentence is: If the decision has been
16 made to discontinue treatment, medications should be
17 tapered as rapidly as is feasible.

18 Do you see that?

19 **A.** I do.

20 **Q.** Do you agree this contemplates taking the patient off
21 of fluvoxamine and doing it as rapidly as feasible?

22 Correct?

23 **A.** As is feasible.

24 **MR. KLEIN:** I have no further questions for the
25 witness.

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1 **THE COURT:** All right. Redirect.

2 **MR. COBLENTZ:** Mr. Brooks, if you could bring
3 up JTX-33 and specifically look at the Indications and
4 Uses section, please.

5 REDIRECT EXAMINATION

6 **BY MR. COBLENTZ:**

7 **Q.** Do you recognize JTX-33 as the Apotex label?

8 **A.** I do.

9 **Q.** And is the Smith-Magenis syndrome present in the
10 Indications and Usage section of this label?

11 **A.** No.

12 **Q.** And if we go to JTX-30 and go to the Indications and
13 Usage section, is JTX-30 Teva's label?

14 **A.** Yes.

15 **Q.** And is the Smith-Magenis syndrome indication in
16 Teva's label?

17 **A.** No, it is not.

18 **Q.** Now, I'd like to, in JTX-30, highlight the Dosage
19 Administration section on Page 1.

20 Now, you were asked questions about the administer at
21 the same time every night.

22 Do you remember that?

23 **A.** I do.

24 **Q.** And do you know if this was from Vanda's clinical
25 trial?

Winkelman - Redirect

1 **A.** Yeah. The reason it's here in the label, just to be
2 clear, is because this was the methodology of the
3 protocol. When you do your clinical trials, having done a
4 lot of clinical trials for studies that are approved, you
5 need to be careful in your protocol because you are making
6 your bed for your label. So what you do in your protocol
7 determines what you are going to see in your label.

8 So this was -- patients were told to do this in the
9 protocol, it's a reasonable thing to tell people to do,
10 but that's why we see it here in the label.

11 **Q.** And in Vanda's clinical trial, they measure sleep
12 parameters and entrainment parameters; is that correct?

13 **A.** Yes.

14 **Q.** And the entrainment parameters were the aMT6s or
15 cortisol?

16 **A.** That's correct.

17 **Q.** And were those -- was that data presented in the
18 label, the aMT6s and cortisol data?

19 **A.** No, no. Nothing about them.

20 **Q.** If we go to JTX-30, Page 9, and the first paragraph,
21 you were asked some questions about the melatonin
22 acrophase in the first paragraph.

23 Do you remember that?

24 **A.** I do.

25 **Q.** And this was in reference to the study 2, the RESET

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1 study; is that correct?

2 **A.** That's correct.

3 **Q.** When was this melatonin acrophase that's referred to
4 here in the label, when was that measured?

5 **A.** At the beginning on entry into the study. They had
6 to have this even to get into the study. They had to have
7 a stable melatonin acrophase.

8 **Q.** What data from the RESET study was presented in the
9 label from the results of that RESET study?

10 **A.** The sleep data. We already looked at that Table 3.
11 Only sleep data.

12 **Q.** So there was no melatonin acrophase data presented
13 from the results of the RESET study in the label; is that
14 correct?

15 **A.** No. They presented this melatonin data here at the
16 beginning of the study. But at the end of the study, the
17 outcomes, the endpoints, the data, if you will, is sleep
18 data, not melatonin data. Sorry.

19 **MR. COBLENTZ:** I have nothing further.

20 **THE COURT:** Okay. I have a couple questions,
21 Doctor.

22 About how many Non-24 patients do you think
23 there are in the United States?

24 **THE WITNESS:** Not a lot.

25 **THE COURT:** I mean, I realize --

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1 **THE WITNESS:** 10,000 something.

2 **THE COURT:** Okay. So it's a very rare disease.

3 **THE WITNESS:** It is.

4 **THE COURT:** To your knowledge, are all of the
5 folks who suffer from the disease blind?

6 **THE WITNESS:** I think it is a complicated
7 question because --

8 **THE COURT:** It's the definition of blind,
9 maybe? I don't know why. Why is it complicated?

10 **THE WITNESS:** No, no. Because in clinic when
11 you see patients, you see a lot of people who -- you know,
12 we looked at those graphics. We see a lot of people who
13 will go like that (indicating). They are not all -- they
14 appear to have a Non-24 period, but -- and they may -- but
15 they are not blind people, so...

16 **THE COURT:** So there are people who suffer from
17 Non-24 that are not blind?

18 **THE WITNESS:** The real Non-24 is blind people.
19 In clinic, you see this pattern of sleep delaying;
20 delaying, delaying that can be not due to lack of photic
21 input for a variety of reasons --

22 **THE COURT:** Well, if I'm in med school and I
23 have a class on Non-24, what are they going to tell me?
24 Who are they going to say suffer from that?

25 **THE WITNESS:** They are going to talk about

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1 blind people.

2 **THE COURT:** Blind people, right?

3 So blindness is defined as Non-24 in that
4 context?

5 **THE WITNESS:** In that context, yes.

6 **THE COURT:** And it is a cause of Non-24 in that
7 context?

8 **THE WITNESS:** Yeah.

9 **THE COURT:** Have you ever prescribed Hetlioz?

10 **THE WITNESS:** Honestly, maybe once. But I --
11 it's possible, but, no, there are other ways of treating
12 this.

13 **THE COURT:** Are you familiar with people in
14 your practice who prescribe it?

15 **THE WITNESS:** We have case series, you know,
16 every week where we talk about patients and, you know,
17 difficult patients and so forth. I've never heard anybody
18 bring up Hetlioz.

19 You know, you never know what doctors and
20 patients are doing, but no.

21 I mean, I treat this Non-24 in blind people by
22 using melatonin.

23 **THE COURT:** Do you prescribe Ambien?

24 **THE WITNESS:** Oh, yeah.

25 **THE COURT:** And this is a little tough for you,

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1 but -- I apologize in a way, but do you know Ambien, the
2 label says its indications and usage are?

3 **THE WITNESS:** Yeah. For the treatment --
4 probably for the treatment of chronic insomnia
5 characterized by -- I'm just paraphrasing -- characterized
6 by difficulty falling or staying asleep.

7 **THE COURT:** So you don't think it's indicated
8 or on the label for a specific disorder; is that right?

9 **THE WITNESS:** Well, now, the -- I'd have to
10 look at the data.

11 **THE COURT:** And that's what's not fair, I
12 guess.

13 What is a disorder? In other words, is there a
14 DSM? Like, are you familiar with -- what's it called?

15 **THE WITNESS:** DSM-5.

16 **THE COURT:** Right. DSM-5, right, is the
17 latest? Okay. So that's got a glossary or, you know, has
18 definitions for various types of diseases, right? I don't
19 know if it encompasses disorder.

20 Do you have a definition of "disorder," what
21 that means?

22 **THE WITNESS:** Well, like in the DSM-5, it has
23 to produce significant impairment. So like OCD.

24 **THE COURT:** Is OCD a disorder?

25 **THE WITNESS:** OCD is a disorder. The "D" is

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1 disorder.

2 **THE COURT:** Okay.

3 **THE WITNESS:** You can have -- you know, people
4 will say -- and I will ask them, have you been diagnosed
5 with OCD? And they say, well, my wife thinks I have OCD
6 because I am also in the garage putting things in order.

7 And I say, well, does it interfere with your
8 life functionally?

9 No.

10 Does it take up a lot of time?

11 No.

12 Well, so that you have obsessive-compulsive
13 tendencies. But obsessive-compulsive disorder has to --
14 disorders have to interfere with functioning, maybe, or
15 feelings.

16 **THE COURT:** All right. But who decides what's
17 a disorder?

18 Is anxiety a disorder?

19 **THE WITNESS:** Anxiety is a symptom. There are
20 a variety of anxiety disorders.

21 **THE COURT:** Okay. And who decides? In other
22 words, do I go to the DSM-5 and how do I figure this out?
23 Is there a body within medicine that says, this is a
24 disorder?

25 **THE WITNESS:** Oh, yeah. There is a nosology

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1 body. I was on the nosology -- head of the nosology
2 committee for sleep medicine for a number of years.

3 Yeah, it is a body of -- a group of people sit
4 around and make decisions about whether something
5 qualifies as a disorder.

6 **THE COURT:** So what body decided that Non-24
7 was a disorder?

8 **THE WITNESS:** I would imagine it was the --
9 this is after I was involved with it -- International
10 Classification -- it's in the International Classification
11 of Sleep Disorders, ICSD, now in its third edition.

12 And so, again, a bunch of specialists decided
13 that this was a disorder.

14 **THE COURT:** All right. Thank you.

15 **THE WITNESS:** You're welcome.

16 **THE COURT:** All right. Next.

17 **MR. ROZENDAAL:** Your Honor, it's video time
18 again.

19 **THE COURT:** So what do we have the rest of the
20 day?

21 **MR. ROZENDAAL:** What we have -- let's see.
22 Seventeen plus seven, 25 minutes of video, and then we
23 have our -- Dr. Perni, our chemistry expert.

24 **THE COURT:** Is he invalidity?

25 **MR. ROZENDAAL:** Well, I suppose he's invalidity

1 and to the extent there is rebuttal of infringement,
2 although it sounds like the facts on the accused processes
3 are pretty clear.

4 **THE COURT:** At least on one thing. I think
5 there is some dispute. It's a summary judgment,
6 essentially, right?

7 **MR. GROOMBRIDGE:** Your Honor, what I was
8 thinking was that there are some claim construction issues
9 here, and I was assuming that Mr. Rozendaal is to address
10 those, given the comments --

11 **THE COURT:** Oh, I think he might. But my point
12 is, I think it's undisputed that there's no contact with
13 the acid.

14 **MR. GROOMBRIDGE:** I think that -- the sequence
15 of steps, I believe, is absolutely --

16 **THE COURT:** Yeah, that's what I meant. But I
17 think that's all that counts. Now, it depends on how I
18 construe the claim.

19 **MR. GROOMBRIDGE:** Exactly, Your Honor.

20 **THE COURT:** It's hard. I will tell you. I
21 did, over lunch, look at the patent. I think you have a
22 very, very big hill to climb. The English is pretty
23 clear. So I will be interested to see and hear argument
24 on all this.

25 All right. Let's do this. So why don't we

1 take a break. We will come back at 3:00.

2 (Whereupon, a recess was taken.)

3 **MR. ROZENDAAL:** Your Honor, may I approach with
4 some binders?

5 **THE COURT:** Please.

6 **MR. ROZENDAAL:** Defendants call as their next
7 witness Dr. Deepak Phadke, who was Vanda's corporate
8 representative. He is vice president for manufacturing at
9 Vanda, and he is a named inventor on the '465 patent.

10 (Video played)

11 **"Q.** All right. Dr. Phadke, can you please state your
12 full name for the record.

13 **"A.** My full name is Deepak Shripad Phadke.

14 **"Q.** When did Vanda first begin investigating those
15 potential impurities formed during the synthesis of
16 tasimelteon?

17 **"A.** I think the general time frame is maybe 2006.

18 **"Q.** Okay. Are you familiar with something called the ICH
19 Guidelines?

20 **"A.** Yes.

21 **"Q.** And do the ICH Guidelines include a specification for
22 the maximum amount of an identified impurity that can be
23 present in an API sample?

24 **"A.** I believe yes.

25 **"Q.** And do you know what that is?

1 "A. It's 0.15.

2 "Q. 0.15 percent?

3 "A. Yeah.

4 "Q. If a chemist was presented with an API sampled, and
5 wanted to determine if an identified impurity was present
6 or not present, what experiment would be done?

7 "A. Drug substance lots are analyzed using analytical
8 methods, such as HPLC or GC and based, and, I guess,
9 from -- from those data, it is possible to understand if
10 impurities are present and what their amounts are. And
11 based on those estimates, then -- and their -- and, I
12 guess, their amounts, then, I guess, we decide if it's
13 necessary to identify an impurity or -- or not.

14 "Q. Okay. Is it fair to say that the chemists who work
15 at pharmaceutical companies, such as yourself -- and
16 you've worked with, I think, Merrell, Merrell, Dow, Rorer,
17 and then as a consultant at Beckloff, that chemists that
18 work at those companies are familiar with the ICH
19 Guidelines?

20 "A. Generally, yes.

21 "Q. Is it -- is it a document the ICH Guidelines
22 something you would have consulted during your time
23 working at Beckloff or at Vanda?

24 "A. Yes.

25 "Q. So what background knowledge about the compound did

1 BMS transfer over to Vanda as part of the agreement?

2 "A. We received research and development reports from BMS
3 that they had, I guess, prepared.

4 "Q. And did BMS transfer over its manufacturing process
5 to Vanda?

6 "A. We received manufacturing process information.

7 "Q. Okay. And would that have -- what would that have
8 entailed, as far as documents, that BMS would have sent to
9 Vanda?

10 "A. Such as development chemistry reports,
11 specifications, analytical methods.

12 "Q. Okay. Did you receive any certificates of analysis
13 from BMS?

14 "A. I believe yes.

15 "Q. And at this point, did BMS also transfer over the
16 IND, Investigational New Drug Application?

17 "A. I believe so, yes.

18 "Q. And Exhibit 6, Doctor, is an e-mail dated
19 September 27th, 2005, and it bears Bates Number
20 VNDHTLZ01048341. And Exhibit 7 is an attachment to that
21 e-mail bearing Bates Numbers VNDHTLZ01048342 through
22 48350. And it appears that the e-mail, Doctor, Exhibit 6,
23 is from a gentleman named David Pereira?

24 "A. Yes.

25 "Q. And if we turn to Exhibit 7, the first page there,

1 this is -- is it fair to say that this is a synthetic
2 scheme that BMS had developed? This is on Page 1 of
3 Exhibit 7.

4 **"A.** It seems that way, yes. It's -- yeah.

5 **"Q.** Okay. And just to clarify, this IND Amend 2 route,
6 is this -- was this a route -- this is shown on Page 3 --
7 was this a route that was developed by BMS or was it
8 developed by Dr. Pereira?

9 **"A.** Based on this document, it appears this was BMS work.

10 **"Q.** I'm going to hand you Exhibit 15 here, Doctor. And
11 this is a document bearing Bates numbers -- this is a
12 document bearing Bates Numbers VNDHTLZ01024384 through
13 4413.

14 **"A.** Yes.

15 **"Q.** Do you recognize this document?

16 **"A.** Yes.

17 **"Q.** What is it?

18 **"A.** Part of NDA submission.

19 **"Q.** This is titled: Manufacturing Process Development.
20 Do you see that?

21 **"A.** Yes.

22 **"Q.** For Process 1 and Process 2, that was -- those were
23 just BMS; is that right?

24 **"A.** Appears that way, yes.

25 **"Q.** Same thing for Process 3; is that right?

1 "A. This is 1998. So this compound was, I guess, under
2 BMS ownership at that time, yes.

3 "Q. I hand you Exhibit 24, which is a document bearing
4 Bates Number VNDHTLZ01101236 through 01101260.

5 Do you recognize this document, Doctor?

6 "A. Yes.

7 "Q. What is it?

8 "A. It is about impurities in tasimelteon drug substance.

9 "Q. Was this a document that was submitted to the FDA?

10 "A. I believe so, yes.

11 "Q. And what's the purpose of this document?

12 "A. It describes impurities in tasimelteon drug substance
13 that's part of the NDA CMC sections.

14 "Q. Exhibit 26 is a document bearing Bates Numbers
15 VNDHTLZ00808239 through 00808260.

16 "A. Yes.

17 "Q. Do you recognize this document, Doctor?

18 "A. Yes.

19 "Q. And what is it?

20 "A. It's one of the CMC sections on drug substance
21 information on justification of specifications for
22 tasimelteon drug substance.

23 "Q. Is this a document that Vanda submitted to the FDA?

24 "A. Yes.

25 "Q. So if there's a specification for the API, is the

1 purpose of this document to provide an explanation or
2 justification of why that is there?

3 "A. Yes.

4 "Q. So I wanted to look with you at Exhibit 24, Doctor,
5 which is the impurities --

6 "A. Yes.

7 "Q. Okay. And if I could draw your attention to
8 Exhibit 24, the same page ending in Bates Number 1244,
9 there is Impurity 5 with a -- that's at the top of that
10 table.

11 "Do you see that, Doctor?

12 "A. Yes.

13 "Q. And afterwards, there's another parenthetical. It
14 says: Impurity P5. Does that indicate that it was first
15 identified by BMS?

16 "A. I believe so, yes.

17 "Q. That was yes?

18 "A. Yes.

19 "Q. I want you to do the same exercise for Impurity 5.
20 If you could compare Column 20, line -- beginning around
21 Line 50 of the '977 patent, which has the chemical name
22 for Impurity 5, is that the same chemical entity that's
23 identified as Impurity 5 in Vanda's NDA for Hetlioz?

24 "A. Yes, I believe so.

25 "Q. Can you pull from the pile of documents, Doctor,

Phadke Video Clip

1 Exhibit 26, please?

2 "A. Yes.

3 "Q. And that's the justification of specification --

4 "A. Uh-huh, yes.

5 "Q. -- that we looked at earlier?

6 "A. Uh-huh.

7 "Q. Okay. So if we could turn to the page -- Page 8 of
8 the document, which is at -- ends in Bates Number 8246.

9 "A. Yes.

10 "Q. There's a section titled, 5.1.12., Impurities. Do
11 you see that?

12 "A. Uh-huh, yes.

13 "Q. Okay. And I want to look at the beginning -- at the
14 last paragraph on the same page. It begins with: Studies
15 have been performed at Formosa, Shasun, BMS and Sai Life
16 Sciences Limited. Do you see that?

17 "A. Uh-huh, yes.

18 "Q. To identify impurities of degradation products found
19 in their respective drug substance lots tested during the
20 release, retest and/or stability testing. Do you see
21 that?

22 "A. Yes.

23 "Q. The document goes on to say: Only those impurities
24 at the identification threshold level of 0.10 percent or
25 greater were identified as Shasun per ICHQ3AR2 Guideline;

1 is that right?

2 "A. Yes.

3 "Q. And is the ICHQ3A Guideline the same ICH Guideline
4 that we discussed earlier today?

5 "A. It's one of the ICH Guidelines, yes.

6 "Q. And this is a guidance for impurity levels in active
7 pharmaceutical drug substances?

8 "A. Yes.

9 "Q. Okay. So your first work related to the tasimelteon
10 was sometime in 2004?

11 "A. Yes.

12 "Q. Have you ever worked for BMS?

13 "A. No.

14 "Q. If you ran just HPLC, would that tell you what
15 impurities you have?

16 "A. You will know; you will know there are impurities,
17 but by simply doing HPLC, you will not know what their
18 chemical structure.

19 "Q. Why not?

20 "A. Because HPLC gives you separation of compounds and
21 their retention times, but it doesn't say anything about
22 their structure.

23 "Q. So the analytical tests to test for impurities will
24 pick up impurities that are unknown, and then you can go
25 back and try and figure out what they were?

Phadke Video Clip

1 "A. I think that's -- that's true generally, yes.

2 "Q. I'm handing you what's marked as Exhibit 47.

3 "A. Uh-huh.

4 "Q. Have you seen this document before?

5 "A. It's very likely that I -- I have, yes.

6 "Q. Why do you say that?

7 "A. Because I reviewed a number of documents from BMS.

8 "Q. Have you, yourself, ever synthesized tasimelteon?

9 "A. Myself?

10 "Q. Yes.

11 "A. No.

12 "Q. Do you know if Natalie Platt has ever synthesized
13 tasimelteon?

14 "A. To the best of my knowledge, no.

15 "Q. Do you know if Ravi Panda -- Pandrapragada has ever
16 synthesized tasimelteon?

17 "A. I don't think so.

18 "Q. Do you know if anyone at Vanda has ever synthesized
19 tasimelteon?

20 "A. I don't think so.

21 "Q. Have you ever analyzed tasimelteon for any
22 impurities?

23 "A. Myself?

24 "Q. Yourself, yes. Sorry.

25 "A. No, I have not.

1 "Q. Do you know if Natalie Platt has ever analyzed
2 tasimelteon for any impurities?

3 "A. No. I don't think so, no.

4 "Q. Do you know if Ravi Pandrapragada has ever analyzed
5 tasimelteon for impurities?

6 "A. I don't think so, no.

7 "Q. Do you know if anyone at Vanda has ever analyzed
8 tasimelteon for impurities?

9 "A. I don't think so.

10 "Q. Tasimelteon was known prior to your invention, right?

11 "A. Yes.

12 "Q. Do you know who initially came up with the idea of
13 tasimelteon?

14 "A. BMS.

15 "Q. And you did not come up with the idea of treating
16 circadian rhythm disorders with tasimelteon, correct?

17 "A. Correct, yes.

18 "Q. Okay. Ways to synthesize tasimelteon were known
19 prior to 2013, correct?

20 "A. They were known, yes.

21 "Q. And BMS had synthesized tasimelteon prior to 2013,
22 correct?

23 "A. Yes.

24 "Q. Analyzing tasimelteon via HPLC for impurities was
25 known prior to 2013, correct?

1 **"A.** Yes.

2 **"Q.** Does that not more than 0.15 percent come from the
3 ICH Guidelines you were discussing earlier?

4 **"A.** For those impurities that were identified, yes.

5 **"Q.** Why did you -- why did the numbers, the 0.15 percent
6 for identified impurities and 0.10 percent for
7 unidentified impurities, why did you want to use ICH
8 Guidelines for setting those limits?

9 **"A.** Because those levels are considered as, you know, for
10 regulatory review. They are considered as appropriate for
11 identified and unidentified impurities.

12 **"Q.** Does -- does the FDA require the use of the ICH
13 Guidelines for the impurity levels?

14 **"A.** I will say generally, yes.

15 **"Q.** Here's a document that's been marked as Exhibit 48.
16 Do you recognize this document?

17 **"A.** I believe so. I have seen this before, yes.

18 **"Q.** What is this document?

19 **"A.** This is from BMS. This is about their IND submission
20 and some questions that Ravi asked them.

21 **"Q.** Is this part of the information that BMS provided to
22 Vanda when Vanda purchased tasimelteon?

23 **"A.** Yes.

24 **"Q.** And here's a document that's been marked Exhibit 49.
25 And do you recognize this document?

Phadke Video Clip

1 **"A.** Yes.

2 **"Q.** What is this document?

3 **"A.** This is a briefing book for the pre-NDA CMC meeting.

4 **"Q.** What did you say again? It's a briefing book for?

5 **"A.** For the pre-NDA CMC meeting we had with the FDA.

6 **"Q.** Is this a document made by Vanda?

7 **"A.** Yes.

8 **"Q.** Is it -- was it submitted to the FDA?

9 **"A.** Yes, it was.

10 **"Q.** And then one more. This document has been marked as
11 Exhibit 50. Do you recognize this document?

12 **"A.** Is it the same document as this, as the...

13 **"Q.** It may be a more complete version with the --

14 **"A.** Yeah.

15 **"Q.** -- cover page.

16 **"A.** Yes. That's what it looks like, yeah. But,
17 otherwise, table of contents information looks similar,
18 so...

19 **"Q.** It looks like the pages are different, though.
20 Exhibit 49 has 110 -- it says Page 110 out of 110. And 15
21 is -- goes up to Page 88 of 88.

22 **"A.** Maybe this is the final version, it's possible.

23 **"Q.** Did Vanda direct BMS to do any work related to
24 tasimelteon?

25 **"A.** No.

1 **"Q.** So BMS's identification of Impurities 4, 5 and 7 was
2 not at Vanda's direction; is that correct?

3 **"A.** I need to look at the structures of 4, 5, 7 to ensure
4 that I understand the question correctly. But the
5 structure identification work that was done at BMS was
6 done on their own. Vanda did not instruct them to do
7 that.

8 **MR. ROZENDAAL:** Your Honor, defendants move the
9 admission of DTX-69, DTX-83, DTX-86, DTX-90, DTX-366,
10 DTX-367, DTX-377, and DTX-383.

11 **MR. GROOMBRIDGE:** No objection.

12 **THE COURT:** All right. They're admitted.
13 (DTX-69, DTX-83, DTX-86, DTX-90, DTX-366,
14 DTX-367, DTX-377, and DTX-383 admitted into evidence.)

15 **MR. ROZENDAAL:** May I approach with binders?

16 **THE COURT:** Please.

17 **MR. ROZENDAAL:** Defendants call by video
18 deposition as their next witness Natalie Farris, who is a
19 named inventor on the '465 patent. Her name appears on
20 the face of the patent as Natalie M. Platt.

21 (Video is played.)

22 **"Q.** So could you please state your full name for the
23 record.

24 **"A.** Natalie Maria Farris.

25 **"Q.** And it says here you managed the analytical method

1 validation at multiple contract laboratories?

2 "A. Correct.

3 "Q. And what were your responsibilities for managing
4 analytical method validation?

5 "A. So this was -- we were entering Phase III clinical
6 studies. And per ICH Guidelines, we have to have methods
7 appropriately validated for that phase of the clinical
8 studies, which means full validation per ICH Guidelines,
9 which is basically that the methods have to be ready for
10 commercialization. So at two companies, I worked with
11 them to make sure that the validation of both of the
12 methods went smoothly, went well. So we had, again,
13 weekly calls. What was happening, how was it -- how was
14 it going? Because prior to Phase III, they're not
15 required to be fully validated. And so minimal validation
16 had to be done, which was -- which worked fine. Once you
17 go to full validation, sometimes things would happen, and
18 it just doesn't work the same, because there, you're
19 looking at a lot more stringent criteria.

20 "Q. And that validation did not deviate from the ICH
21 Guidelines?

22 "A. Correct.

23 "Q. So did you use a laboratory notebook at all when you
24 were at Vanda?

25 "A. No.

1 "Q. So did you not perform any experiments at Vanda?

2 "A. No.

3 "Q. Did you do method development and optimization at
4 Vanda?

5 "A. I helped manage the development and optimization of
6 methods at Vanda.

7 "Q. So what did that entail? How is it different from
8 actually doing the method validation?

9 "A. So that is where we work closely with the third-party
10 vendor to try and understand what problems are -- are
11 coming up, and how to fix those problems. So having my
12 background in chemistry lab, or the quality control lab,
13 and knowing the instruments, I was able to help in the
14 optimization and problem with troubleshooting at the
15 company.

16 "Q. But the initial design for the methods and the
17 eventual optimization, that was done by the third-party
18 vendor?

19 "A. Yes.

20 "Q. You also reviewed cost proposals from potential CMOs,
21 and I believe recommended and selected CMOs, as well; is
22 that correct?

23 "A. Correct.

24 "Q. What are CMOs?

25 "A. Contract manufacturing organizations.

1 "Q. And that would include companies such as Shasun and
2 Formosa?

3 "A. Correct.

4 "Q. Did you review any of Formosa's or Shasun's
5 proposals?

6 "A. Yes.

7 "Q. And you made recommendations based off of them?

8 "A. Yes.

9 "Q. If a proposal was accepted, would you -- would Vanda,
10 then, enter into an agreement?

11 "A. Yes.

12 "Q. And this is during -- this is just ordinary business
13 practice, correct?

14 "A. Correct.

15 "Q. Did you develop any of the validation protocols, or
16 were you just in the role of approving them?

17 "A. Reviewing and approving.

18 "Q. But not developing?

19 "A. No.

20 "Q. Did Vanda have any labs?

21 "A. They had no working labs when I joined. So since I
22 joined, they had no working labs.

23 "Q. Are you familiar with the term "virtual company"?

24 "A. Yes.

25 "Q. Was Vanda a virtual company?

1 "A. Yes.

2 "Q. So BMS was the first manufacturer of tasimelteon?

3 "A. Yes.

4 "Q. And you had no involvement with developing methods of
5 identifying the impurities; is that correct?

6 "A. Correct.

7 "Q. And you had no involvement with quantifying
8 impurities; is that correct?

9 "A. Correct.

10 "Q. And this is a document beginning with Bates Number
11 VNDHTLZ-01-1069-6, and it continues through 2724. Do you
12 recognize this document?

13 "A. Yes.

14 "Q. And what is it?

15 "A. It is a Module II section from the US NDA.

16 "Q. And the statement that begins the following
17 paragraph: BMS fully characterized tasimelteon as
18 reported in the initial IND submission submitted
19 December 17th, 1997. Is that also accurate?

20 "A. Yes.

21 "Q. Do you recognize this document?

22 "A. Yes.

23 "Q. And what is this?

24 "A. It's the corresponding Module III section for the
25 characterization in the US NDA.

1 "Q. So is it fair to say that these impurities, 1 through
2 7 that are identified in this NDA section, were all
3 identified by either Formosa, Shasun or BMS?

4 "A. Yes.

5 "Q. Thank you. Okay. I will now hand you what has been
6 previously marked as defendants' Exhibit 20. Do you
7 recognize this document?

8 "A. Yes.

9 "Q. And what is this?

10 "A. The patent.

11 "Q. If we go back for a moment to Claim 24 of the patent,
12 it states: Purified tasimelteon, wherein the tasimelteon
13 does not contain any of the following impurities at a
14 concentration greater than 0.15 percent. Do you know why
15 0.15 percent was chosen?

16 "A. 0.15 percent was chosen based on ICH Guideline. And
17 to -- basically if we state that it's an identified
18 impurity, which is -- by doing the testing that I had
19 mentioned earlier, then we can bring the specification up
20 to .15 percent. If not, if it's still an unknown
21 impurity, it's still controlled at 0.10 percent.

22 **MR. ROZENDAAL:** Your Honor, we move the
23 admission of DTX-1, DTX-80 and DTX-83.

24 **MR. GROOMBRIDGE:** No objection.

25 **THE COURT:** All right. They're admitted.

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(DTX-1, DTX-80, DTX-83 admitted into evidence.)

MS. WELLS: Our next, defendants call

Dr. Robert Perni.

THE COURT: Okay.

THE CLERK: Please raise your hand, and state
and spell your name for the record.

THE WITNESS: My name is Robert Perni,
R-O-B-E-R-T, P-E-R-N-I.

Robert Perni, having been called as a witness, being
first affirmed or duly sworn under oath, testified as
follows:

THE CLERK: You may be seated.

DIRECT EXAMINATION

BY MS. WELLS:

Q. Good afternoon, Dr. Perni.

A. Good afternoon.

Q. Would you please introduce yourself to the Court?

A. Yes. My name is Robert Perni. I'm a chemist, and I
have been in the pharmaceutical business for a long time.

Q. Have you prepared some demonstratives to assist with
your testimony today?

A. I have.

MS. WELLS: Mr. Brooks, can you please pull up
Dr. Perni's demonstratives.

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BY MS. WELLS:

Q. Dr. Perni, could you turn in your binder to Tab DTX-401?

A. Okay.

Q. Do you recognize DTX-401?

A. Yes, I do.

Q. What is this document?

A. It is my CV.

Q. Does it accurately reflect your education and experience?

A. It does.

MS. WELLS: Move to admit DTX-401 into evidence.

MR. GROOMBRIDGE: No objection.

THE COURT: All right. It's admitted.

(DTX-401 admitted into evidence.)

BY MS. WELLS:

Q. Dr. Perni, could you please describe your educational background?

A. Yes. I have a bachelor's degree in chemistry from Northeastern University. I followed that up with doctoral studies at Dartmouth College, where I obtained my Ph.D. And I have postdoctoral appointments at the University of Rochester in the chemistry department.

Q. What was your professional experience after

1 schooling?

2 **A.** So I spent my entire career in the biopharmaceutical
3 business at a number of organizations with positions of
4 increasing responsibility, leading up to my current
5 position as vice president of R&D at IM Therapeutics.

6 **Q.** In the course of your career, have you played any
7 role in the drug development?

8 **A.** Excuse me. Yes, I have.

9 **Q.** Could you provide an example?

10 **A.** At Vertex, I was a discovery project head, and I
11 headed up, at the time, the hepatitis C program where we
12 identified a clinical candidate. And not only headed up
13 the team, I headed up the med-chem group that synthesized
14 the compound.

15 When that compound went into development, I was on
16 the development team to assist in the development of the
17 manufacturing method.

18 **Q.** Did your work as Vertex lead to FDA approval?

19 **A.** Yes. That drug was approved in 2011.

20 **Q.** Did your responsibilities in any of your positions
21 involve testing for impurities in the drug substance?

22 **A.** Yes, in all of my positions.

23 **Q.** Through your experience, are you familiar with the
24 drug manufacturing approval process and requirements?

25 **A.** I am.

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1 Q. Have you published any articles or do you have any
2 patents relating to development of pharmaceutical
3 products?

4 A. I do.

5 Q. Dr. Perni, can you provide the Court with an overview
6 of the testimony that you intend to give today?

7 A. Yes. So today, I'm going to give a brief overview
8 and background of the '465 patent, as well as my opinion
9 on the noninfringement of that patent, as well as its
10 invalidity.

11 Q. Is there particular prior art you believe would have
12 rendered the asserted claim of the '465 patent obvious?

13 A. Yes. I would cite CN268 patent, in combination with
14 the ICH Guidelines as rendering the claim obvious.

15 Q. Do you have any other prior art combination that you
16 believe renders the claim obvious?

17 A. Yes, I would cite patent '529, in combination with
18 the ICH Guidelines.

19 Q. You also have what's listed here "improper
20 inventorship."

21 What do you mean by that?

22 A. The '465 patent, from my reading, incorporates some
23 fundamental work that was done at BMS. And so the fact
24 that there's no BMS inventors is problematic.

25 Q. All right. Thank you.

1 Let's start with your overview and background of the
2 '465 patent.

3 **A.** Yes.

4 **Q.** At a high level, what is your understanding of the
5 subject matter of the '465 patent?

6 **A.** It's the manufacturing with high purity
7 pharmaceutical grade tasimelteon.

8 **Q.** And what is the title of the '465 patent?

9 **A.** In fact, it's highly purified pharmaceutical grade
10 tasimelteon.

11 **Q.** Do you have an understanding of the claim that is
12 asserted in this case?

13 **A.** I do.

14 **Q.** And what claim is that?

15 **A.** It's Claim 10, as it depends on Claim 1.

16 **Q.** What does Claim 10, which depends on Claim 1, cover?

17 **A.** It covers the two -- the final two steps of the
18 preparation of tasimelteon, as well as an impurity profile
19 for that final product.

20 **Q.** What are the two claimed manufacturing steps?

21 **A.** The two steps are the reduction of the compound on
22 the top left, referred to as the carboxamide. And
23 reduction step to the methanamine. And then subsequent,
24 propionylation of the methanamine to the final tasimelteon
25 product.

~~Perni~~ Direct

1 Q. You mentioned impurities.

2 What is an impurity in the context of a drug
3 substance like tasimelteon?

4 A. In this case, the impurity would refer to side
5 products. These are undesirable products that form in the
6 reaction. And those are generally removed in a general
7 sense, but there's often small amounts that are difficult
8 to remove. And these are referred to as "impurities."

9 Q. In your opinion, is it important to quantify the
10 impurities that are present in a drug substance?

11 A. Absolutely. It is essential.

12 Q. Why?

13 A. These are drugs. These are for human consumption.
14 And so the safety of the material can be compromised if
15 there's excessive levels of other compounds in there.

16 Q. How do you go about quantifying impurities?

17 A. Typically, they're quantified by high performance
18 liquid chromatography.

19 Q. Did you prepare a demonstrative to aid in your
20 discussion of high performance liquid chromatography?

21 A. I did.

22 Q. How does high performance liquid chromatography, or
23 HPLC, work?

24 A. So HPLC is a separation technique where a substance
25 is placed on a column. In this particular case, the

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1 column has a flowing solvent under a high pressure that
2 moves the material down, what's referred to as a solid
3 phase, that the material you placed on it interacts.

4 Different components will travel through at different
5 speeds. When they come off, they are detected
6 electronically. And they're represented by a graph that
7 takes into account the time it comes off, as well as the
8 relative amount of the material.

9 **Q.** Does HPLC tell you whether you have impurities?

10 **A.** It tells you whether or not you have impurities, yes.

11 **Q.** Does HPLC tell you the percentage or concentration of
12 each impurity you have?

13 **A.** Yes, it does.

14 **Q.** Are you familiar with the term "identification" of an
15 impurity?

16 **A.** Yes.

17 **Q.** What does it mean for an impurity to be identified?

18 **A.** For an impurity to be identified, it means structural
19 identification of the -- of that particular impurity.

20 **Q.** Does HPLC tell you the structural identity of an
21 impurity?

22 **A.** No. There's no structural information in HPLC.

23 **Q.** So is impurity detection equivalent to impurity
24 identification?

25 **A.** No.

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1 Q. Is it fair to say HPLC will detect that you have an
2 impurity and at what concentration without telling you the
3 structural identity of that impurity?

4 A. That is correct.

5 Q. How sensitive is HPLC at detecting impurities?

6 A. It can be very sensitive under ideal conditions. It
7 can detect impurities down to below .01 percent.

8 Q. Does the '465 patent say the test that can be run to
9 detect Impurities 1 through 3, 5 and 6?

10 A. Yes. It actually specifies high performance liquid
11 chromatography.

12 Q. Does the '465 patent list any specific conditions or
13 parameters for the HPLC analysis to detect Impurities 1
14 through 3, 5 and 6?

15 A. No, it does not.

16 Q. If the '465 patent doesn't list the specific
17 parameters for the HPLC analysis, how will a skilled
18 artisan know how to detect Impurities 1 through 3, 5 and
19 6?

20 A. The development of a chromatography method for any
21 drug really entails a standard process that an analyst
22 would simply know. Based on the structure of your drug,
23 an analyst would know what sort of column to use. There
24 is certainly trial and error, but there's a standard
25 routine that one goes through to develop the process.

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1 Q. Is developing an optimized HPLC conditions within the
2 purview of those skilled in the art?

3 A. That's the job.

4 Q. Are you aware that after learning of Vanda's patent
5 claims discussing specific impurities, the FDA inquired
6 whether Teva and Apotex's analysis was capable of showing
7 the presence of those impurities?

8 A. Yes, I am.

9 Q. Does the FDA's inquiry change your view that
10 developing and optimizing HPLC conditions is within the
11 purview of those skilled in the art?

12 A. No, it does not.

13 Q. Why would the FDA inquire about those impurities?

14 A. My understanding was the FDA was aware of those
15 impurities. And so being a regulatory agency, they were
16 just checking to make sure that, you know, those
17 particular impurities had been controlled for.

18 Q. Do you have an understanding of what Teva and
19 Apotex's, tasimelteon manufacturers, did in response to
20 the FDA inquiry?

21 A. I believe they performed spiking experiments where
22 they actually added samples of those impurities to the -
23 to the drug to show that the method could, in fact, detect
24 them.

25 Q. And were the experiments able to show that if

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1 Impurities 1 through 3, 5 and 6 had been present in the
2 sample, that the HPLC would have detected them?

3 **A.** Yes.

4 **Q.** So no changes were required to the HPLC analysis in
5 order to detect those impurities?

6 **A.** As far as I know, that's true.

7 **Q.** Now, are you aware of any changes that were required
8 to the manufacturing process for Teva or Apotex in view of
9 the FDA's inquiry regarding these impurities?

10 **A.** No.

11 **Q.** Is it fair to say that scientists working on Teva and
12 Apotex's tasimelteon were able to develop a method of
13 making tasimelteon in which Impurities 1 through 3, 5 and
14 6 were kept below 0.15 percent without even being aware of
15 the impurities?

16 **A.** Yes.

17 **Q.** And is it also fair to say that the scientists were
18 able to develop an HPLC method capable of detecting these
19 impurities without ever having been aware of the
20 impurities?

21 **A.** Yes.

22 **Q.** Dr. Perni, do you have any reason to doubt that a
23 skilled artisan, as of February 2014 priority date, would
24 have known how to develop and optimize HPLC conditions,
25 such that the presence of Impurities 1 through 3, 5 and 6

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1 would be detected?

2 **A.** No. I have no reason to believe that.

3 **Q.** Were you in the courtroom for yesterday's testimony?

4 **A.** Yes, I was.

5 **Q.** And did you hear that --

6 **THE COURT:** Can you stop for a second?

7 **MS. WELLS:** Sure.

8 **THE COURT:** So the question was: Do you have
9 any reason to doubt that a skilled artisan, as of
10 February 2014, would have known how to develop an
11 optimization HPLC conditions, such that the presence of
12 Impurity 1 through 3, 5 and 6 would be detected, and you
13 said you have no reason to believe that?

14 **THE WITNESS:** I have no reason to doubt that.

15 **THE COURT:** Okay. Just want to make sure. All
16 right. Thank you.

17 **THE WITNESS:** Apologies, Your Honor.

18 **THE COURT:** No, no. You don't need to
19 apologize. But I know that I'm going to have briefs and
20 I'm going to read this, and I didn't think that's what you
21 meant to say. But that's good.

22 **MS. WELLS:** Thank you for the clarification.

23 **THE COURT:** I have the luxury of a transcript
24 going in front of me; you don't. So thanks.
25

1 **BY MS. WELLS:**

2 **Q.** Did you hear the testimony about the structure of
3 Impurities 1 through 3, 5 and 6?

4 **A.** Yes.

5 **Q.** Do either of Claims 1 or 10 of the '465 patent
6 require knowledge of the structural identity of Impurities
7 1 through 3, 5 and 6?

8 **A.** No.

9 **MR. GROOMBRIDGE:** Objection, Your Honor. We
10 seem to be getting into legal conclusions here.

11 **THE COURT:** All right. Hold on a second.
12 What do you think, Ms. Wells?

13 **MS. WELLS:** I think he's reading the claims
14 from the perspective of a POSA and trying to bring to
15 light what they mean to someone skilled in the art at the
16 time.

17 We seem to have a bit of a potential dispute
18 about whether impurity identification refers to actual
19 structural identification or just identification in the
20 lay sense, meaning detection.

21 **THE COURT:** Why don't you break it down? Maybe
22 that's the way to approach it as opposed to just an
23 overview question. Does that make sense? There is a fine
24 line, right, with all these experts?

25 **MS. WELLS:** Sure. I can ask a different

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1 question.

2 **THE COURT:** I think that would be good, yes.

3 **BY MS. WELLS:**

4 **Q.** Dr. Perni, in your opinion, do you need to know the
5 structure of Impurities 1 through 3, 5 and 6 in order to
6 make tasimelteon with less than 0.15 of each of them?

7 **A.** No, you do not.

8 **Q.** If someone doesn't know the structural identity of
9 Impurities 1 through 3, 5 and 6, is there a way for them
10 to know whether the tasimelteon that they have produced
11 has any of those impurities above 0.15?

12 **A.** Well, if there are no peaks above 0.15 percent, then
13 by definition, none of these impurities can be present at
14 greater than 0.15 percent.

15 **Q.** Let's move on to your opinion regarding infringement,
16 which I think we can short circuit a little bit.

17 Were you in the courtroom this morning when
18 Dr. Bergeimer provided his infringement opinion?

19 **A.** I was.

20 **Q.** Do you agree with Dr. Bergeimer that the hydrochloric
21 acid that Teva and Apotex processes never contacts or
22 reacts with the carboxamide?

23 **A.** I do.

24 **Q.** In view of this, what is your opinion on whether Teva
25 and Apotex infringe Claim 10 of the '465 patent?

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1 **A.** I do not believe that they do infringe.

2 **Q.** And if we could turn to the next slide, let's take a
3 look at the claim language.

4 What have you highlighted in blue here on the
5 demonstrative?

6 **A.** So I've highlighted the first step of the two-step
7 process that the patent talks about. It's the reduction
8 of the carboxamide.

9 **Q.** And have you prepared a cartoon demonstrative to
10 illustrate what you believe the claim requires?

11 **A.** Yes.

12 So the obvious reading of the claim to me is that you
13 take the carboxamide, the reducing agent and the acid, and
14 you combine them in a single reaction vessel together.

15 **Q.** Okay. And do you recall that Dr. Bergeimer, when
16 discussing this claim limitation, discussed the schematic
17 from the '465 patent?

18 **A.** Yes.

19 **MS. WELLS:** Mr. Brooks, if we could pull up
20 JTX-6, and Column 13, Scheme 5 there.

21 **THE WITNESS:** Yep.

22 **BY MS. WELLS:**

23 **Q.** Dr. Perni, what is Scheme 5 from the '465 patent
24 showing?

25 **A.** Scheme 5 is the reduction of the carboxamide with

1 lithium aluminum hydride followed by addition of HCL and
2 ethanol and a TBME to give the methanamine hydrochloride.

3 **Q.** Is there a reducing agent shown in Scheme 5?

4 **A.** Yes, it is. Lithium aluminum hydride.

5 **Q.** Would you ever react lithium aluminum hydride with an
6 acid?

7 **A.** No, you would not.

8 **Q.** Why not?

9 **A.** If the -- the acid would immediately destroy the
10 lithium aluminum hydride.

11 **Q.** Could it even ignite and cause a fire?

12 **A.** High probability.

13 **Q.** Is lithium aluminum hydride the only reducing agent?

14 **A.** No. This process could be affected with a number of
15 reducing agents.

16 **Q.** Are reducing agents a class of compounds?

17 **A.** They are.

18 **Q.** Are there other reducing agents, not lithium aluminum
19 hydride, that you could put in the same reaction mixture
20 with an acid and carboxamide to form methanamine?

21 **A.** Yes.

22 **Q.** And doing it that way, mixing the reducing agent, the
23 acid, and the carboxamide all together, could that
24 potentially have an impact on the yield of the
25 methanamine?

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1 **A.** It could.

2 **Q.** So is it fair to say it may not be optimal to mix all
3 three together, but it is possible to do it that way
4 depending on the specific reagent --

5 **A.** Depending on the specific reducing agent, the
6 specific acid, yes, that would be possible.

7 **Q.** We can take that down.

8 We can short circuit the rest of noninfringement and
9 move on to your invalidity opinions.

10 **MS. WELLS:** I believe, Mr. Brooks, it starts on
11 Slide 14.

12 **BY MS. WELLS:**

13 **Q.** Dr. Perni, do you have an opinion on what the
14 experience and education would have been for a skilled
15 artisan in the context of the '465 patent?

16 **A.** Yes, I do.

17 So typically in the pharmaceutical business, such a
18 skilled artisan would have a PhD in organic or medicinal
19 chemistry or a related field and been in the business
20 several, several years; alternatively, a very talented
21 bachelor's and master's degree scientists that have
22 somewhat greater experience that would also be considered
23 skilled artisans.

24 **Q.** And I would like to draw particular attention to the
25 bottom half because I believe this might be where you have

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1 a dispute with Dr. Bergeimer.

2 What is the qualification that you are listing on the
3 bottom half of the screen.

4 **A.** That they would have been -- that they would have
5 known and been aware of regulatory requirements concerning
6 drug manufacturing. It's hard to see how one can work in
7 pharmaceutical drug manufacturing and not have that
8 knowledge.

9 **Q.** Is there a difference between the level of impurities
10 that are permitted in pharmaceutical products compared to
11 other compounds?

12 **A.** Typically, yes. The regulatory requirements for
13 pharmaceuticals are generally much stricter than for
14 industrial chemicals.

15 **Q.** Did you prepare a timeline to aid your testimony here
16 today?

17 **A.** Yes, I did.

18 **Q.** Dr. Perni, what are you showing happened in 1997 on
19 your timeline?

20 **A.** In 1997, Bristol-Myers Squibb filed the IND for
21 tasimelteon.

22 **Q.** And what is an IND?

23 **A.** An IND is an investigational new drug application.
24 It's where all the data from the research phase of drug
25 discovery is pulled together. It's submitted to the FDA.

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1 Approval of an IND allows dosing of the drug in clinical
2 trials to human beings.

3 Q. What are you showing in 1998?

4 A. In 1998, BMS manufactured lot C028B.

5 Q. Is there a particular significance to lot C028B?

6 A. Yes. It is a high purity lot that was in one of the
7 more advanced versions of the manufacturing process BMS
8 had developed.

9 Q. What are you showing happening in 1999 on your
10 timeline?

11 A. In 1999, the '529 patent actually issued.

12 Q. And what happened in 2004?

13 A. 2004, Bristol-Myers licensed the drug to Vanda.

14 Q. Did BMS provide Vanda with its tasimelteon
15 manufacturing specifications?

16 A. Yes, it did.

17 Q. Did BMS also provide Vanda with certificates of
18 analysis for the tasimelteon that BMS had manufactured?

19 A. Yes, it did.

20 Q. What happened in 2006 on your timeline?

21 A. So the current version of the ICH Guidelines were
22 published in 2006 that set the criteria for impurities.

23 Q. What happened in 2012 on your timeline?

24 A. 2012 was the publication of the '268 -- CN268 patent.

25 Q. The last entry on your timeline is 2014. What

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happened in 2014?

A. So that was the priority date for the '465 patent application.

Q. What is your understanding of the relevant time period for the invalidity analysis for the '465 patent?

A. So it's before 2014.

Q. Dr. Perni, do you have an understanding of who first discovered tasimelteon?

A. Yes.

Q. Who is that?

A. That was BMS.

Q. Do you have an understanding of who first synthesized tasimelteon?

A. Scientists at BMS.

Q. Do you have an understanding of who first conceived of using tasimelteon in a pharmaceutical product?

A. BMS.

Q. Do you have an understanding of who filed the tasimelteon IND with the FDA?

A. BMS.

Q. Let's take a look at that IND. If we can turn to the next demonstrative, we have an excerpt from JTX-117 at Page 3.

Can you explain what is shown on JTX-117, Page 3?

A. So this is specifically referring to batch C028B,

1 where they're basically saying that by doing some small
2 modifications to the existing manufacturing process, they
3 were able to generate this particular lot that met their
4 impurity specifications.

5 **Q.** Let's take a look at that modified synthesis.

6 This slide is an excerpt from JTX-117, Page 6.

7 And what are we looking at here, Dr. Perni?

8 **A.** So we're looking at the two-step manufacturing
9 process in 1998.

10 So the first step was the formation of the
11 carboxamide material for the last two steps. And that
12 carboxamide is, it's reduced and the methanamine
13 intermediate in the middle was then propionylating to give
14 tasimelteon which is shown in the bottom right.

15 **Q.** How does the carboxamide in BMS's process compare to
16 the carboxamide in Claim 1 on the '465 patent?

17 **A.** It is one and the same.

18 **Q.** How does the methanamine in BMS's process compare to
19 the methanamine in Claim 1 of the '465 patent?

20 **A.** It's the same compound.

21 **Q.** In order to get from the carboxamide to the
22 methanamine, what did BMS do?

23 **A.** BMS performed a reduction step with the reducing
24 agent shown in orange, which is a related reducing agent
25 to lithium aluminum hydride, and subsequently treated in a

1 second step with hydrochloric acid to form a methanamine
2 salt.

3 **Q.** And then what happens to the methanamine salt in
4 BMS's process in order to get tasimelteon?

5 **A.** So in this process, methanamine is treated with
6 propionyl chloride to give tasimelteon.

7 **Q.** Is propionyl chloride a propionylating reagent?

8 **A.** It is.

9 **Q.** How does the process BMS used to synthesize
10 tasimelteon compare to the processes that Teva and Apotex
11 use?

12 **A.** They're essentially the same.

13 **Q.** If you apply Dr. Bergmeier's reading of Claim 1 to
14 allow for the sequential reaction of a reducing agent
15 followed by an acid, how does the process that BMS used to
16 synthesize tasimelteon compare to the process in Claim 1
17 of the '465 patent?

18 **A.** Well, under that interpretation, this would be the
19 same.

20 **Q.** You mentioned earlier batch C028B which you said was
21 made according to this process. How can you tell if that
22 was made according to this process?

23 **A.** Because it said so. I believe that's in the IND.

24 **Q.** So we're at the Slide JTX-117, Page 12. And what are
25 you illustrating there?

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1 **A.** So this is a statement that says that that is the
2 method that was used to prepare C028B.

3 **Q.** Can you tell from BMS's IND when batch C028B was
4 synthesized?

5 **A.** Yes. It shows the date of February of 1998.

6 **Q.** Did BMS analyze the purity of the tasimelteon
7 synthesized in batch C028B?

8 **A.** Of course.

9 **Q.** What method did they use to analyze the purity of the
10 C028B batch?

11 **A.** They used HPLC.

12 **Q.** That's the same method we talked about earlier?

13 **A.** Yes, it is.

14 **Q.** And the same HPLC method referred to in the '465
15 patent?

16 **A.** It is.

17 **Q.** What were the results of BMS's HPLC analysis of batch
18 C028B?

19 **A.** So it resulted in a very high purity batch with a
20 HPLC purity of 99.9 percent and a total impurity content
21 of 0.15 percent.

22 **Q.** What does the total impurity content of 0.15 percent
23 mean?

24 **A.** It means that if you combine the amounts of all the
25 impurities that are detected and summed them together,

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1 that's the sum.

2 **Q.** Does the total impurity in BMS batch C028B of 0.15
3 percent tell you anything about the level of each of
4 Impurities 1 through 3, 5 and 6?

5 **A.** Yeah. It says by definition if the total is 0.15,
6 none of those individually can exceed 0.15.

7 **Q.** Did BMS tell Vanda about the purity of batch C028B
8 and how it was manufactured?

9 **A.** Yes.

10 **Q.** Why do you say that?

11 **A.** It was in the IND, and I believe it was also provided
12 in the licensing agreement.

13 **Q.** Is there any indication from Vanda's own NDA that
14 Vanda was aware of batch C028B?

15 **A.** Yes. It's specifically referred to.

16 **Q.** So on slide -- we're showing Page 13 of DTX-73. What
17 is being shown on Page 13?

18 **A.** So on the far right is -- it shows several batches on
19 the page. But C028B is shown on the far right highlighted
20 in yellow, and it lists all the impurities that had been
21 detected previously.

22 And as you can see, there are only two impurities
23 that had been specific impurities that had been detected
24 and the rest were nondetectable, which is -- and the total
25 impurity content is 0.15 percent.

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1 So it's consistent with the previous statements.

2 Q. What does "ND" stand for?

3 A. Not detected.

4 Q. What does that mean?

5 A. It means that the HPLC did not show a peak at that --
6 or at very least, it was below 0.05 percent.

7 Q. Did Vanda's NDA say anything about BMS's work related
8 to impurity identification?

9 A. Yes.

10 So specifically, they mentioned that Impurity P5 from
11 BMS was correlated to their Impurity 5, and that BMS had
12 run MS and NMR on that particular impurity.

13 Q. So you are looking at DTX-73, Page 8. And you
14 mention that it says LCMS and LCNMR.

15 What are LCMS and LCNMR?

16 A. So LC refers to liquid chromatography. So they do a
17 separation to isolate the -- to separate out the impurity
18 individually.

19 And then mass -- the MS is mass spectrum --
20 spectrometry, which is a technique for showing the mass of
21 the molecule, the total molecule, the weight of the
22 molecule.

23 NMR is nuclear magnetic resonance. That's a
24 technique, it's a relatively complex technique, but it
25 gives you information on the structural connectivity of

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1 the atoms in the molecule so that the NMR data combined
2 with mass spectral data is typically how one deduces the
3 structure of the impurity.

4 **Q.** Were you in the courtroom yesterday when
5 Mr. Pandrapragada testified?

6 **A.** Yes, I was.

7 **Q.** Did you hear him testify that LCMS and NMR are common
8 tools for identifying structure of impurity?

9 **A.** Yes.

10 **Q.** Do you agree with that statement?

11 **A.** Absolutely.

12 **Q.** Is impurity P5 one of the impurities that's discussed
13 in the '465 patent?

14 **A.** Yes.

15 **Q.** Why do you say that?

16 **A.** Because it specifies that it is. It shows Impurity
17 P5 as Impurity 5. This is what -- I mean, Vanda specified
18 this to the FDA.

19 **Q.** You are referring to DTX-73, Page 7?

20 **A.** Yes.

21 **Q.** Who are the named inventors on the '465 patent?

22 **A.** So the named inventors are Deepak Phadke, Natalie
23 Platt and Ravi Pandrapragada.

24 **Q.** Were any of these three individuals involved with
25 BMS's tasimelteon work?

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1 **A.** No.

2 **Q.** Dr. Perni, to summarize your opinion on the improper
3 inventorship, was the named inventors on the '465 patent
4 the first to conceive of a process of synthesizing
5 tasimelteon?

6 **A.** No.

7 **Q.** Were the named inventors the first to conceive of
8 synthesizing tasimelteon by reacting carboxamide first
9 with a reducing agent and then with an acid in an organic
10 solvent to yield methanamine?

11 **A.** No.

12 **Q.** Were the named inventors the first to conceive of
13 synthesizing tasimelteon by reacting methanamine with a
14 propionylating reagent to yield tasimelteon?

15 **A.** No.

16 **Q.** Were the named inventors the first to conceive of
17 synthesizing tasimelteon with less than 0.15 percent of
18 each of Impurities 1 through 3, 5 and 6?

19 **A.** No.

20 **Q.** Were the named inventors the first to discover each
21 Impurities 1 through 3, 5 and 6?

22 **A.** No.

23 **Q.** Who, in your view, conceived of synthesizing
24 tasimelteon meeting these requirements before the named
25 inventors?

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1 **A.** BMS.

2 **Q.** Thank you.

3 We discussed earlier how HPLC can be run to determine
4 the quantity of each impurity, and you walked us through a
5 demonstrative?

6 **A.** Yes.

7 **Q.** The one on the screen.

8 Once HPLC determines the quantity of each impurity,
9 what do you do next?

10 **A.** So you would compare them to the ICH guidelines. And
11 if impurities exceeded 0.15 percent, typically you would
12 do a reprocessing step to get the impurity below that
13 level.

14 **Q.** Can you please turn in your binder to DTX- 55.

15 **A.** Okay.

16 **Q.** Do you recognize DTX- 55?

17 **A.** Yes, this is the Q3A ICH guideline.

18 **MS. WELLS:** Move to introduce DTX- 55 into
19 evidence.

20 **THE COURT:** Any objection?

21 **MR. GROOMBRIDGE:** No objection.

22 **THE COURT:** It's admitted.

23 (DTX-55 admitted into evidence.)

24 **BY MS. WELLS:**

25 **Q.** Dr. Perni, when was the ICH Q3A guideline published?

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1 **A.** It was published in 2006.

2 **Q.** Prior to February 2014, was this ICH Q3A guideline
3 sufficiently accessible to skilled artisans?

4 **A.** Yes.

5 **Q.** What exactly is the ICH?

6 **A.** The ICH is the International Counsel for
7 Harmonization. It's a group of regulatory representatives
8 from the United States, the European Union and Japan that
9 got together to create a single series of requirements to
10 aid in the drug approval process across international
11 borders.

12 **Q.** Does the USFDA recognize the ICH guidelines?

13 **A.** Yes, it does.

14 **Q.** Do people working in the pharmaceutical industry on
15 drug development consider the ICH Q3A guideline?

16 **A.** Yes.

17 **Q.** Were you, yourself, familiar with the ICH guidelines
18 in your work outside of this case?

19 **A.** Yes.

20 **Q.** Does the ICH Q3A guideline provide information
21 related to impurities?

22 **A.** Yes, it does.

23 **Q.** What information does the ICH Q3A guideline provide
24 related to impurities?

25 **A.** It gives you guidance for how to handle impurities at

1 different concentrations.

2 **MS. WELLS:** Mr. Brooks, if we can turn to slide
3 30.

4 **BY MS. WELLS:**

5 **Q.** Dr. Perni, on Slide 30, we have an excerpt of
6 attachment one, which is from Page 12 of DTX- 55.

7 Can you explain what is shown in attachment one of
8 the ICH guideline?

9 **A.** Yes. So this table is taken directly from the ICH
10 guideline. So there are two rows that are based on the
11 amount of drug that's actually dosed to a person. Because
12 tasimelteon is given in milligram quantities, only the
13 first row really applies. But it indicates that there's
14 reporting threshold and identification threshold and
15 qualification threshold.

16 So what that means is that for any peak in the HPLC
17 that is below 0.05 percent, it does not need to be
18 reported. You do not need to put it in the list of
19 impurities. So it's .02 percent; you can effectively
20 ignore it. From 0.05 percent up, you need to report the
21 presence of that impurity, and it's reported by retention
22 time.

23 If the amount of the impurity exceeds .1 percent,
24 then you need to actually identify what that impurity is.
25 If then the amount of impurity exceeds 0.15 percent, then

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1 additional testing is generally required, because it's
2 felt that impurities above that level could affect the
3 safety. So therefore, you'd have to obtain the impurity
4 in pure form either by isolation or synthesis, and then
5 run a series of safety experiments, the specifics of which
6 would be dependent on the specific drug.

7 **Q.** You mentioned the three thresholds that are shown
8 here, and I'd like to go through them each individually.

9 The first one you mentioned was a reporting
10 threshold. What does reporting mean?

11 **A.** Reporting means that you note the presence of the
12 impurity, and that's noted by retention time only.

13 **Q.** Does the structure need to be determined?

14 **A.** No.

15 **Q.** And then the next threshold you mentioned was an
16 identification threshold.

17 What happens there?

18 **A.** So there not only is the retention time reported, but
19 the structure needs to be identified.

20 **Q.** Is any additional safety testing required?

21 **A.** Not at that point, no.

22 **Q.** The final threshold that you mentioned was the
23 qualification threshold?

24 **A.** Yes.

25 **Q.** What does qualification mean?

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1 **A.** It means -- it refers to safety qualification, that
2 the impurity has been looked at for safety considerations
3 and shown to be safe.

4 **Q.** In your opinion, is there an incentive or motivation
5 to try to keep impurities below the 0.15 percent
6 qualification threshold?

7 **A.** Yes. Qualification thresholds can be a fairly long
8 and expensive process, and so it -- and possibly with
9 significant risk to the product, because it could turn out
10 that the impurity is, in fact, not safe.

11 So qualifying an impurity is something that you want
12 to try to avoid as often as possible.

13 **Q.** If you run HPLC and detect that you have an impurity
14 present above 0.15 percent, is there anything you can do
15 to try and avoid this regulatory burden?

16 **A.** You can repurify that particular batch of material,
17 yes.

18 **Q.** Dr. Perni, do the ICH guidelines discuss tasimelteon
19 or any other Impurities 1 through 3, 5 or 6 in particular?

20 **A.** Not specifically, no.

21 **Q.** If the guidelines don't discuss tasimelteon or these
22 particular impurities, would someone interested in making
23 tasimelteon even consider the ICH guidelines?

24 **A.** Yes, they would.

25 **Q.** Why?

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1 **A.** Because they want to get the drug approved for sale.
2 So if you want approval, you need to follow the
3 guidelines.

4 **Q.** Thank you.

5 Let's turn to your opinions regarding the application
6 of the ICH guideline in this case. What is the first
7 prior art reference to which you applied the ICH
8 guidelines?

9 **A.** So that would be CN268 in combination with the
10 guidelines.

11 **Q.** What is your opinion of the validity of Claim 10 of
12 the '465 patent in view of CN268 and the ICH guidelines?

13 **A.** Combination of the two I believe renders the claim
14 invalid.

15 **Q.** Can you, please, turn in your binder to DTX- 301.

16 **A.** Okay.

17 **Q.** Do you recognize DTX- 301?

18 **A.** Yes. It's the '268 patent.

19 **MS. WELLS:** Move to introduce DTX- 301 into
20 evidence.

21 **MR. GROOMBRIDGE:** No objection.

22 **THE COURT:** It's admitted.

23 (DTX-301 admitted into evidence.)

24 **BY MS. WELLS:**

25 **Q.** Dr. Perni, when was CN268 published?

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1 **A.** It was published in September of 2012.

2 **Q.** Prior to the February 2014 priority date of the '465
3 patent, was CN268, in your opinion, sufficiently
4 accessible to skilled artisans?

5 **A.** Yes.

6 **Q.** Would a skilled artisan seeking to synthesize
7 tasimelteon look to CN268?

8 **A.** Yes.

9 **Q.** Why?

10 **A.** They describe a method for manufacturing high purity
11 tasimelteon, so you would want to see what they did.

12 **Q.** Does CN268 disclose whether tasimelteon is useful as
13 a pharmaceutical?

14 **A.** Yes, it is disclosed in the background information.
15 It specifically talks about sleep onset latency and, you
16 know, its use.

17 **Q.** You're reading from Paragraph 2 of CN268; is that
18 correct?

19 **A.** Correct.

20 **Q.** Does CN268 discuss any advantages of making
21 tasimelteon according to the process it discloses?

22 **A.** Yes. It refers -- it refers to the process as
23 being -- as providing fewer side reactions, and
24 consequently affording higher purity product.

25 **Q.** Does CN268 disclose a composition comprising

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1 tasimelteon?

2 **A.** Yes, it does.

3 **MS. WELLS:** Mr. Brooks, if we could turn to
4 Slide 40, please.

5 **BY MS. WELLS:**

6 **Q.** Dr. Perni, does CN268 include any examples showing
7 the synthesis of tasimelteon?

8 **A.** Yes, it does.

9 **Q.** Is one of those examples shown on Paragraphs 41
10 through 46, which are reproduced on the demonstrative?

11 **A.** Yes.

12 **Q.** What is the final product of Paragraph 46 of CN268?

13 **A.** It is tasimelteon.

14 **Q.** Does CN268 say anything about the purity of the
15 tasimelteon that was obtained?

16 **A.** Yes. It clearly shows it was 99.5 percent pure.

17 **Q.** Does CN268 say whether the scientists could confirm
18 whether they had, in fact, synthesized tasimelteon?

19 **A.** Yes.

20 **Q.** Doctor, if we turn to Slide 41, which has an excerpt
21 from the end of Paragraph 46 from CN268, what exactly,
22 Dr. Perni, does CN268 say about the final product?

23 **A.** It states that it could be confirmed that the product
24 obtained was tasimelteon.

25 **Q.** Do the reported yield or melting point lead you to

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1 doubt that the reaction in CN268 formed tasimelteon?

2 **A.** I have no doubt that tasimelteon was formed.

3 **Q.** Does CN268 include any other examples of synthesizing
4 tasimelteon?

5 **A.** Yes, it does.

6 **MS. WELLS:** If we could turn to Slide 43,
7 Mr. Brooks.

8 **BY MS. WELLS:**

9 **Q.** Slide 43 has Paragraph 63 and 64 from CN268.

10 Dr. Perni, what is the product -- final product
11 that's produced in Paragraph 63 and 64?

12 **A.** It's tasimelteon.

13 **Q.** Does CN268 say anything about the purity of this
14 batch of tasimelteon that was produced?

15 **A.** Yes. This particular batch was 99.6 percent pure.

16 **Q.** Does CN268 refer specifically to any of Impurities 1
17 through 3, 5 or 6?

18 **A.** No, it does not.

19 **Q.** If CN268 does not discuss Impurities 1 through 3, 5
20 and 6, would a skilled artisan, in your opinion, have been
21 motivated to make tasimelteon using the process described
22 in CN268 with limits on these impurities?

23 **A.** Yes.

24 **Q.** What limits would a skilled artisan have applied?

25 **A.** It would -- a skilled artisan would have invoked the

1 ICH Guidelines and set limits of 0.15 percent for any
2 impurity.

3 **Q.** What would have motivated a skilled artisan to apply
4 the 0.15 percent threshold in the ICH Guideline to the
5 tasimelteon synthesis described in CN268?

6 **A.** Again, it's a regulatory threshold. And the idea is
7 to get a drug approved.

8 **Q.** As of the February 2014 priority date of the '465
9 patent, would a skilled artisan have a reasonable
10 expectation of success in applying the 0.15 percent
11 threshold from the ICH Guidelines to the tasimelteon
12 synthesis in CN268?

13 **A.** Yes, absolutely.

14 **Q.** Why?

15 **A.** Given that the products were of -- you know, purities
16 were -- there's only a half a percent or so total
17 impurity. That, alone, makes it likely that no individual
18 impurity is greater than 0.15 percent.

19 But in the event that there was one or more
20 impurities greater than 0.15 percent, at that point, it's
21 fair to believe that one would be able to purify it a
22 little bit further to get it down below that level.

23 **Q.** Thank you.

24 Let's turn now to your second obviousness opinion.

25 What is the second piece of prior art to which you

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1 applied the ICH Guideline?

2 **A.** So I combined the BMS '259 patent with ICH
3 Guidelines.

4 **Q.** And what is your opinion of the validity of Claim 10
5 in view of the '529 patent and the ICH Guidelines?

6 **A.** Again, in combination of a -- the combination of ICH
7 Guidelines with '529, I believe, renders Claim 10 as
8 obvious.

9 **Q.** When did the '529 patent issue?

10 **A.** '529 patent issued in January of 1999.

11 **Q.** Prior to the February 2014 priority date of the '465
12 patent, was the '529 patent, in your opinion, sufficiently
13 accessible to skilled artisans?

14 **A.** Yes.

15 **Q.** As of February 2014, would a skilled artisan seeking
16 to develop a process for synthesizing tasimelteon have
17 looked to the '529 patent?

18 **A.** Yes.

19 **Q.** Why?

20 **A.** It was the first synthesis of '529, and that's where
21 you would start.

22 **Q.** You said it was the first synthesis of '529?

23 **A.** I'm sorry, of tasimelteon. And then that's -- you
24 would start that as your basis of preparing.

25 **Q.** Does the '529 patent discuss compositions that

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1 include tasimelteon?

2 **A.** Yes.

3 **Q.** Does the '529 patent say anything about tasimelteon
4 for pharmaceutical products?

5 **A.** Yes, it does. It specifically discusses it in terms
6 of it being a melatonin agonist and it's for sleep
7 disorder.

8 **Q.** And you are looking in particular at the '529 patent,
9 which is DTX-12, Column 2, in your reading, I think,
10 starting at Line 3 on the demonstrative?

11 **A.** Yes, that's correct.

12 **Q.** Let's turn to Example 2 of the '529 patent.

13 What is the final product that's being synthesized in
14 Example 2 of the '529 patent?

15 **A.** It is tasimelteon.

16 **Q.** And do you know who filed for and owns the '529
17 patent?

18 **A.** Bristol-Myers Squibb.

19 **Q.** Does the '465 patent itself say anything about
20 Bristol-Myers Squibb's '529 patent?

21 **A.** It actually cites it, yes, in the background.

22 **Q.** And on the screen here, we have an excerpt from the
23 back under the invention of the '465 patent, which is
24 JTX-6.

25 What exactly is the '465 patent saying here?

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1 **A.** It's disclosing that tasimelteon was prepared in the
2 '529 patent, and that the final step was the
3 propionylation of the methanamine with propionyl chloride.

4 **Q.** Does the '529 patent refer specifically to any of
5 Impurities 1 through 3, 5 or 6?

6 **A.** No, it does not.

7 **Q.** If the '529 patent does not discuss these impurities,
8 would a skilled artisan have been motivated to limit the
9 amount of each of these impurities in tasimelteon made
10 using the process described in the '529 patent?

11 **A.** Yes.

12 **Q.** What limit would a skilled artisan have applied?

13 **A.** It would have applied the 0.15 percent limit as
14 dictated by the ICH Guideline.

15 **Q.** What would have motivated a skilled artisan to apply
16 the 0.15 percent limit from the ICH Guideline to the
17 tasimelteon synthesis in the '529 patent?

18 **A.** Because this is a drug that was seeking approval.

19 **Q.** As of the February 2014 priority date of the '465
20 patent, in your opinion, would a skilled artisan have a
21 reasonable expectation of success in applying the
22 0.15 percent threshold from the ICH Guideline to the
23 tasimelteon synthesis in the '529 patent?

24 **A.** Yes.

25 **Q.** To summarize, what is your opinion on the validity of

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1 Claim 10 of the '465 patent?

2 **A.** I believe in light of previous work, in conjunction
3 with ICH Guidelines, it renders it obvious.

4 **MS. WELLS:** Thank you. No further questions.

5 **THE COURT:** All right. Cross.

6 **MR. GROOMBRIDGE:** Yes, Your Honor.

7 May we approach with some binders, Your Honor?

8 **THE COURT:** Yes, please.

9 CROSS EXAMINATION

10 **BY MR. GROOMBRIDGE:**

11 **Q.** Good afternoon, Dr. Perni.

12 **A.** Good afternoon.

13 **Q.** We haven't met. I'm Nicholas Groombridge. It is a
14 pleasure to be acquainted.

15 I'd like to start by just talking about the '465
16 patent and the reaction Scheme 5, about which you were
17 asked on your direct examination.

18 **MR. GROOMBRIDGE:** And, Mr. Weir, could you put
19 up JTX-6, please. And let's go to Column 13.

20 **BY MR. GROOMBRIDGE:**

21 **Q.** And, Dr. Perni, would you agree with me that there's
22 a part of the '465 patent that deals with the reaction,
23 the portion of the synthesis of tasimelteon, which had
24 been our focus here today and yesterday?

25 **A.** Yes.

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1 Q. And that that part of the patent begins at Column 13
2 at around Line 30, and then it goes on through to
3 Column 15 at about Line 25?

4 A. Yes.

5 Q. And that's the section that's dealing with so-called
6 scheme -- Reaction Scheme 5, correct?

7 A. Correct.

8 Q. And that's the only part of the patent specification
9 that's dealing with that reaction scheme, correct?

10 A. I believe so, yes.

11 Q. And if I understand, your view of the patent is that
12 what's disclosed here is not covered by the claim,
13 correct?

14 A. That is correct.

15 Q. And just to be clear, there's nothing else, there's
16 no other alternative reaction scheme in the patent that
17 you believe is covered by the claim.

18 A. Not that I recall, no.

19 Q. And so --

20 MR. GROOMBRIDGE: Now, let's just enlarge the
21 diagram, please. The scheme for the reaction, Mr. Weir.

22 BY MR. GROOMBRIDGE:

23 Q. And as we look at this, we're going from what the
24 patent calls "Intermediate 4," and that is the
25 carboxamide, correct?

1 **A.** Correct.

2 **Q.** To what the patent calls "Intermediate 5," and that's
3 the methanamine, correct?

4 **A.** Correct.

5 **Q.** And that's what is called, in your business, "a
6 reducing step," correct?

7 **A.** Correct.

8 **Q.** And that's because we want to change this structure
9 up in the upper right-hand depiction -- depicted portion
10 of the structure I showed you, to a different structure,
11 correct?

12 **A.** Correct.

13 **Q.** And to do that, we have to engage in a reduction
14 reaction, correct?

15 **A.** Correct.

16 **Q.** And in the context of these particular molecules, we
17 would use a so-called hydride reducing agent, correct?

18 **A.** Yes.

19 **Q.** The one used here is lithium aluminum hydride,
20 correct?

21 **A.** Correct.

22 **Q.** There are others, but they're still hydride reducing
23 agents?

24 **A.** Yes.

25 **Q.** And as depicted here, there are -- above the arrow,

1 it shows the lithium aluminum hydride. And is that
2 tetrahydrofuran?

3 **A.** Yes, it is.

4 **Q.** And that's an organic solvent?

5 **A.** Correct.

6 **Q.** And then below the line, it shows hydrochloric acid?

7 **A.** Yes.

8 **Q.** And an ethanol?

9 **A.** Yes.

10 **Q.** And what's TBME?

11 **A.** Tert-butyl methyl ether.

12 **Q.** What role does that play?

13 **A.** That's a cosolvent to just --

14 **Q.** And then following the -- this scheme, this graphical
15 depiction, there's about a column and a half of text that
16 actually describes in words what's going on, correct?

17 **A.** Correct.

18 **Q.** In some detail.

19 And toward the end of that, it refers to the point at
20 which the hydrogen chloride gets added, correct?

21 **A.** Correct.

22 **Q.** And maybe we can -- just so we orient everyone, let's
23 go to the -- let's just look at Column 14 here, and let's
24 enlarge the top of Column 14. And here in about Lines 8
25 and 9 is where it introduces the reducing agent, correct?

1 **A.** Yes.

2 **Q.** And then there's a fair amount of detail about how
3 the reduction is performed and what those steps taking
4 place, correct?

5 **A.** Correct.

6 **MR. GROOMBRIDGE:** And then if we go to the top
7 of Column 15, please, Mr. Weir, and we'll just enlarge
8 that there.

9 **BY MR. GROOMBRIDGE:**

10 **Q.** We see that at Lines 4 to 6, the reference to
11 hydrogen chloride, correct?

12 **A.** Yes.

13 **Q.** And that's what would be called a "quench," correct?

14 **A.** No, I don't believe that's the quench. Hold on a
15 moment.

16 No, I believe the quench occurs before that.

17 **Q.** Oh, I'm sorry.

18 **A.** I'd like to see the bottom.

19 **Q.** By all means.

20 **A.** Column 14, please.

21 **MR. GROOMBRIDGE:** Yeah. Do you want to blow
22 that up, Mr. Weir. Can we look at the lower part of the
23 Column 14.

24 **BY MR. GROOMBRIDGE:**

25 **Q.** And is there a part in here you would point to for

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1 the quench?

2 **A.** So the -- could I see above that section, because
3 the -- they're talking about distilling off the solvent
4 and stuff. Sorry.

5 **MS. WELLS:** Your Honor, may the witness just be
6 advised that there's a copy of the hard document in the
7 binder?

8 **THE COURT:** He may be advised.

9 **THE WITNESS:** Thank you. Sorry.

10 **THE COURT:** Just by asking the question. But,
11 yes, so you are advised that there is a hard copy of it.

12 **THE WITNESS:** Sorry.

13 **THE COURT:** No, that's fair game. In fact,
14 it's probably easier if --

15 **THE WITNESS:** So this is JTX- which?

16 **MR. GROOMBRIDGE:** Six.

17 **THE COURT:** It's the '465 patent, right?

18 **MR. GROOMBRIDGE:** Yeah.

19 **THE WITNESS:** Column 14.

20 **BY MR. GROOMBRIDGE:**

21 **Q.** In your white binder, it will be the second item, I
22 think.

23 **A.** Yes. I've got it.

24 **Q.** And, Doctor, I don't think --

25 **A.** So the quench occurs halfway down Column 14.

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1 Q. Fair enough. The -- now --

2 THE COURT: When you say "halfway down," for
3 the record, do you mind, what line?

4 THE WITNESS: So where they talk about sodium
5 hydroxide, so that is Line 27.

6 BY MR. GROOMBRIDGE:

7 Q. It starts on Line 27, and then that sentence
8 continues for a bit, correct?

9 A. Yes.

10 Q. And what they are doing there is using sodium
11 hydroxide, the base, as the quench, right?

12 A. Yes. The quench can occur with acid or base. In
13 this case, it's a base.

14 Q. You'd have to do a quench, but you could do it either
15 with an acid or a base, correct?

16 A. Yeah. Typically, if you do it with an acid, you then
17 follow it with base to neutralize, yes.

18 Q. And the purpose of the quench is that you have to get
19 rid of whatever remaining part of the reducing agent
20 that's present; is that right?

21 A. Right.

22 Q. Because you can't -- and would you agree that a
23 person of ordinary skill would know that you cannot
24 perform the reducing step in the presence of an acid?

25 A. With that particular reagent, you cannot perform it

1 in the presence of an acid.

2 Q. And a person of ordinary skill would know also that
3 you would have to do a quench with either an acid or a
4 base before you moved on to try to form a salt, correct?

5 A. Correct.

6 Q. And when you wanted to form the salt, would you
7 typically do that by introducing some other acid, correct?

8 A. Correct.

9 Q. And in this case, it's hydrogen chloride to form the
10 chloride, correct?

11 A. Correct.

12 Q. And so -- and the reason why you would have to be
13 careful here is because these hydride reducing agents are
14 materials that have to be treated with some care, correct?

15 A. Absolutely, yes.

16 Q. In other words, if you just took an acid --
17 particularly, let's say, a strong non-oxidizing acid like
18 hydrogen chloride and dumped it into the reducing stage
19 with the hydride, what would happen?

20 A. If you did it fast enough, it could explode.

21 Q. And every one skilled in the art would know that?

22 A. Absolutely.

23 Q. That's kind of high school chemistry, correct?

24 A. Yes.

25 Q. That if you contact a strong reducing agent with an

~~Perni~~ - Cross

1 acid, you're asking for something very undesirable to
2 happen?

3 **A.** Correct.

4 **Q.** And would you agree, also, that in the reducing step,
5 a person of ordinary skill would know that if you put an
6 acid in at that stage, in the presence of the reducing
7 agent, it would, in essence, prevent the reducing agent
8 from doing its job?

9 **A.** Correct.

10 **Q.** And, again, that's a matter of basic chemistry?

11 **A.** Yes.

12 **Q.** Now, let's talk about the inventorship issues,
13 please, and Bristol-Myers Squibb.

14 And just to be clear, Dr. Perni, you are not pointing
15 to any actual individual at Bristol-Myers Squibb who you
16 say should be coinventor on this patent?

17 **A.** No, I don't have enough information to do that.

18 **Q.** You're inferring that somebody there should be a
19 coinventor, but you don't know who?

20 **A.** That is correct, yes.

21 **Q.** And -- now, were you in the courtroom yesterday when
22 Dr. Pandrapragada testified?

23 **A.** Yes.

24 **Q.** And do you recall that he was asked about whether the
25 P5 that Bristol-Myers Squibb had named was the same as the

~~Perni~~ - Cross

1 Impurity 5 that Vanda had named?

2 Do you remember that?

3 **A.** Yes.

4 **Q.** And just to orient ourselves, we can agree that P5 is
5 a designation that BMS came up with in the late 1990s as
6 part of its work?

7 **A.** Yes.

8 **Q.** And Impurity 5 is a designation that Vanda came up
9 with some years later?

10 **A.** Yes.

11 **Q.** And it's merely coincidence that they both happen to
12 have the digit five in them?

13 **A.** Yes.

14 **Q.** And do you recall that Mr. Pandrapragada testified
15 that when they -- in the FDA submissions, when they lined
16 up Impurity 5 from Vanda and P5 from BMS, they weren't --
17 the relative retention times were not exactly the same?

18 **A.** Yes.

19 **Q.** One of them was 1.48, and the other was 1.50?

20 **A.** Yes.

21 **Q.** And -- but he said, well, we thought that that was
22 close enough for the purposes that we were writing up in
23 that document?

24 **A.** Yes.

25 **Q.** And you're not disagreeing with that, are you?

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1 **A.** No. If you were to run the same experiment on the
2 same machine yourself, you could end up with those numbers
3 with the same material.

4 **Q.** And that's just because there's enough variability
5 and sensitivity in these techniques that you cannot
6 necessarily have confidence in the numbers to the second
7 decimal place?

8 **A.** Correct.

9 **Q.** And -- now, I think you looked -- I know you looked
10 at Vanda's submission as part of its NDA that touched on
11 these issues, and I'd like to briefly go to that.

12 **MR. GROOMBRIDGE:** That's PTX-811, Mr. Weir.
13 Could you put that up, please.

14 Let's just enlarge the uppermost portion of the
15 page, including the header, please.

16 **BY MR. GROOMBRIDGE:**

17 **Q.** And, Dr. Perni, just so we're -- we all know what
18 we're looking at, this is one of the documents about which
19 you testified on your direct examination, correct?

20 **A.** Correct.

21 **Q.** And this is a portion of Vanda's submission to the
22 FDA when it was asking for approval to market tasimelteon?

23 **A.** Correct.

24 **Q.** And this, in particular, deals with the impurities
25 and how they were controlling for the impurities; is that

1 right?

2 **A.** Yes.

3 **MR. GROOMBRIDGE:** And let's go to Page 10,
4 please, Mr. Weir, and enlarge the table -- the table and
5 the text immediately underneath it.

6 **BY MR. GROOMBRIDGE:**

7 **Q.** And, again, just so we're clear, relative retention
8 time was something that we heard about yesterday, correct?

9 **A.** Yes.

10 **Q.** And would you have any disagreement with the
11 testimony that the Court heard yesterday concerning
12 relative retention time?

13 **A.** No.

14 **Q.** So relative retention time is when I'm looking at --
15 when something comes out of the HPLC column, and I'm
16 comparing it to when a standard came out of the column,
17 correct?

18 **A.** Yeah, typically it's the drug.

19 **Q.** The drug. And that's why it's relative, right?

20 **A.** Correct.

21 **Q.** And if the number is greater than one, does that mean
22 it comes off the column after the drug?

23 **A.** If it's greater than one, it comes on after the drug,
24 that's correct.

25 **Q.** And so what we've got here, as far as we're talking

~~Perni~~ - Cross

1 about P5, Impurity 5, it shows that BMS was getting a
2 relative retention time of 1.5 for whatever the material
3 P5 was, correct?

4 **A.** Correct.

5 **Q.** And Vanda's contract manufacturer, Formosa, was
6 getting a relative retention time of 1.4 for that,
7 correct?

8 **A.** Correct.

9 **Q.** And Vanda's other contract manufacturer, Shasun, was
10 not finding it, correct?

11 **A.** Correct.

12 **Q.** And by the way, the -- they, then, told FDA about --
13 summarize the information that they were presenting.

14 They said here: Comparison of the impurity data from
15 three manufacturers shows that the impurity profile has
16 not changed significantly throughout the manufacturing
17 history, except that the impurity levels are much lower in
18 the Formosa and Shasun drug substance lots, as compared to
19 most of the BMS drug substance lots.

20 And would you disagree with that?

21 **A.** No.

22 **Q.** Now, I'd like to look at the BMS regulatory
23 submission from however many years it was, some, I guess,
24 15 or 16 years earlier, and that's JTX-117.

25 And if you need to reference the documents, they are

1 all in the white binder.

2 **A.** Yes, I see it. Thank you.

3 **MR. GROOMBRIDGE:** And, again, Mr. Weir, let's
4 just enlarge the header here so we're oriented.

5 **BY MR. GROOMBRIDGE:**

6 **Q.** And can you confirm that this is part of the
7 so-called investigational new drug application that BMS
8 submitted for tasimelteon?

9 **A.** Yes.

10 **Q.** All right. And that's what it means when it says
11 "IND-54776"?

12 **A.** Yes.

13 **Q.** And this is Submission Number 004.

14 Do you see that?

15 **A.** Yes.

16 **Q.** And it would be typical for there to be multiple
17 submissions, and they would be numbered, increasing over
18 time?

19 **A.** Yes.

20 **Q.** And this document about -- you testified, I think,
21 about this, that it discloses the manufacturing process
22 that BMS was using by this point?

23 **A.** This is the CMC section, yes.

24 **Q.** And just so everyone is clear, that's a different
25 manufacturing process from what is in the BMS patent,

1 correct?

2 **A.** Yes, it is.

3 **Q.** And that would be very normal in the pharmaceutical
4 industry, correct?

5 **A.** Correct.

6 **Q.** Because when you're inventing new molecules, you are
7 interested in making as many different molecules as
8 quickly as you can, right?

9 **A.** Correct.

10 **Q.** That's drug discovery?

11 **A.** Correct.

12 **Q.** And you don't really care about how good the process
13 is?

14 **A.** Correct.

15 **Q.** But when you pick one out and you say, this looks
16 good, I'm going to bring it through, at that point you
17 start wanting to make the process better, right?

18 **A.** Correct.

19 **Q.** As far as we can tell, that's exactly what BMS did
20 here, right?

21 **A.** Well, this isn't a process patent. But they
22 developed a process, yes.

23 **Q.** Sorry. Just to be clear, looking at the -- as far as
24 we can reconstruct based on the information --

25 **A.** Yes.

~~Perni~~ - Cross

1 Q. -- available to us, looking at what BMS was doing in
2 the late 1990s as they took tasimelteon to clinical
3 development, they began to work on the process, correct?

4 A. Correct.

5 Q. And they switched at that point to a process that has
6 the kind of steps we've been talking about where a
7 carboxamide is reduced to form a methanamine, right?

8 A. Correct.

9 Q. And just to be clear, looking at what we've seen
10 here, at no point did BMS ever use a process that, in your
11 view, would be covered by the '465 patent, correct?

12 A. Correct.

13 Q. And are you aware, Dr. Perni, that after BMS made the
14 lot that you talked about on your direct examination, it
15 again changed the manufacturing process?

16 A. I didn't know that, but it wouldn't surprise me.

17 MR. GROOMBRIDGE: Well, let me -- let's look at
18 Page 50 of JTX-117. And let's start by enlarging the
19 header there, please, Mr. Weir.

20 BY MR. GROOMBRIDGE:

21 Q. And do you see this is now part of Submission 007 in
22 the IND?

23 A. Yes.

24 Q. And we can agree that would be later in time than
25 Submission 004, correct?

1 **A.** Yes.

2 **MR. GROOMBRIDGE:** And now, Mr. Weir, let's see
3 if we could just enlarge the table, all of the table that
4 as big as we can get.

5 **BY MR. GROOMBRIDGE:**

6 **Q.** And what we see here is a series of batches that have
7 been made by BMS, correct?

8 **A.** Yes.

9 **Q.** And the last but one, the penultimate, is the one
10 about which you testified on your direct examination,
11 correct?

12 **A.** Yes.

13 **Q.** That's the one for which BMS was reporting a total
14 impurity content of 0.15 percent?

15 **A.** Yes.

16 **Q.** If we look at the earlier batches, would you agree
17 that the impurity level is all a great deal higher for
18 every batch?

19 **A.** Yes.

20 **Q.** And, then, this now contains information for another
21 batch, N030B.

22 Do you see that?

23 **A.** Yes.

24 **Q.** What's the impurity level there?

25 **A.** 0.44 percent.

~~Perni~~ - Cross

1 Q. Now, are you aware of any reason why it is that
2 batch, C028B, would have an impurity level lower than all
3 the ones that were made before it and the one that was
4 made after it?

5 A. I would assume that it's a different process than the
6 ones before it and the ones after it.

7 Q. But other than assumption, do you have any facts to
8 point to as to why that might be?

9 A. Not based on this table.

10 Q. Well, even apart from the table, anything that you've
11 seen in the course of forming your opinions?

12 A. No.

13 Q. Now, would you agree with me, by the way, moving
14 on --

15 MR. GROOMBRIDGE: We can take that down.

16 BY MR. GROOMBRIDGE:

17 Q. -- that BMS actually published information about its
18 process in -- for example, in 2004?

19 A. I'm sorry. Could you restate?

20 Q. Terrible question. Let me try it again.

21 Would you agree with me that BMS made public the fact
22 that it had -- was using a process that contained a step
23 in which a carboxamide was reduced to form a methanamine?

24 A. Yes.

25 Q. And could you tell me when that happened?

1 **A.** Well, that happened with the issuance of the '529
2 patent.

3 **Q.** Let's be clear, I want to make sure we don't -- I
4 think we're in agreement, but tell me if I'm wrong.

5 But the '529 patent does not include such a process?

6 **A.** I'm sorry. I'm confused.

7 **Q.** Probably my fault. Let me try again just to step
8 back and clarify.

9 BMS, we all agree, I think, came up with a molecule
10 tasimelteon in -- sometime in the 1990s, right?

11 **A.** Yes.

12 **Q.** Just an audible answer so the court reporter has it.

13 **A.** Yes.

14 **Q.** Thank you.

15 And following that, they filed a patent application
16 that included tasimelteon and also quite a lot of other
17 potential compounds, right?

18 **A.** Yes.

19 **Q.** That matured into what we have been calling the '529
20 patent, correct?

21 **A.** Correct.

22 **Q.** And that's one -- about one of the things you
23 testified about with Ms. Wells, correct?

24 **A.** Correct.

25 **Q.** And -- but is it the case that the '529 patent, it

1 includes a process for making tasimelteon, but not the
2 process in which a carboxamide is reduced to form a
3 methanamine?

4 **A.** That's correct.

5 **Q.** Now, would you agree with me that BMS then went on,
6 as part of its process development, to create such a
7 process; we've been looking at it in the IND?

8 **A.** Yes.

9 **Q.** At some point after that, they actually made public
10 that one way to get tasimelteon was to go through a
11 synthetic pathway in which you made a carboxamide
12 intermediate and then you reduced it to get a methanamine
13 intermediate?

14 **A.** Yes.

15 **Q.** And so that information was in the public domain long
16 before the '465 patent, correct?

17 **A.** Yes.

18 **Q.** While we're talking about the BMS '529 patent, would
19 you agree with me that it has no reference to purity of
20 the product?

21 **A.** That's correct.

22 **Q.** And it certainly has no reference to Impurities 1, 2,
23 3, 5 or 6, correct?

24 **A.** Correct.

25 **Q.** Now, looking at the -- let's look at the so-called

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1 CN268 reference.

2 **MR. GROOMBRIDGE:** And that is DTX-301, please,
3 Mr. Weir. And let's go to Page 24, the beginning of the
4 translation. I think Page 24, please, using the
5 litigation -- the exhibit numbers. And let's just enlarge
6 the bibliographic information, please. That's good.

7 **BY MR. GROOMBRIDGE:**

8 **Q.** And just again so we're oriented, this is -- this is
9 the CN268 reference, correct?

10 **A.** Correct.

11 **Q.** And it's a patent application in the Chinese Patent
12 Office, correct?

13 **A.** Correct.

14 **Q.** Published, I want to say, September 19, 2012?

15 **A.** Yes.

16 **Q.** And would you agree with me that this does not -- it
17 mentions purity in a couple of places?

18 **A.** Yes.

19 **Q.** But it does not include any other information as to
20 how one would purify tasimelteon?

21 **A.** Correct.

22 **Q.** And just for confirmation, there were three examples
23 given in this patent, are there not?

24 **A.** I believe so.

25 **Q.** And it gives a purity. But the highest -- but the

~~Perni~~ - Cross

1 purest one was the one that you talked about on your
2 direct, which has a purity of 99.6 percent, correct?

3 **A.** Correct.

4 **Q.** And, likewise, this patent doesn't mention Impurities
5 1, 2, 3, 5 or 6, correct?

6 **A.** Correct.

7 **Q.** And now, I'd like to just wrap up by talking about
8 the ICH Guideline.

9 **MR. GROOMBRIDGE:** And can we -- let's pull up,
10 please, DTX-55.

11 **BY MR. GROOMBRIDGE:**

12 **Q.** Dr. Perni, this is the guideline that you've used in
13 your August -- one of the references of obviousness
14 combinations?

15 **A.** Yes.

16 **MR. GROOMBRIDGE:** And let's go to Page 6,
17 please, Mr. Weir. And let's see if we can enlarge --
18 let's start with the section headed 3, Organic Impurities.

19 **BY MR. GROOMBRIDGE:**

20 **Q.** And -- now, would you agree that the type of
21 impurities we're talking about here are organic
22 impurities?

23 **A.** Yes.

24 **Q.** And so this would be the relevant section of the
25 Guideline?

1 **A.** Correct.

2 **Q.** And just so we're clear, the -- I think you touched
3 on this on your direct. But just -- again, so that
4 there's no possibility of confusion, that different levels
5 are called out for either identification or qualification,
6 correct?

7 **A.** Correct.

8 **Q.** And those are terms of art in this field?

9 **A.** Yes. Right.

10 **Q.** And identification that's -- that's -- refers to
11 requirements that come into play when you've got not more
12 than 0.1 percent of the impurity, right?

13 **A.** Correct.

14 **Q.** Whereas, qualification comes into play when you've
15 got not more than 0.15 percent of the --

16 **A.** When you have more than 0.15.

17 **Q.** Oh, I'm sorry. When you have more than 0.15 percent.
18 Sorry.

19 And there are different consequences depending on
20 whether you're working in the identification world or the
21 qualification world?

22 **A.** Correct.

23 **Q.** And I think I heard you to say, but I was just -- to
24 be clear, that you would prefer not to be in the -- in an
25 area where you had to engage in qualification, in other

~~Perni~~ - Cross

1 words, where you were above 0.15, correct?

2 **A.** Yes.

3 **Q.** That's because that can start to get onerous very
4 quickly?

5 **A.** Correct.

6 **Q.** And I think -- looking just a moment about what might
7 be required.

8 But I'll -- now, the Guideline would require the
9 applicant to summarize actual and potential impurities
10 most likely to occur, correct?

11 **A.** Correct.

12 **Q.** And then it goes on to say that the applicant should
13 characterize the structure of actual impurities, correct?

14 **A.** Correct.

15 **Q.** And do we agree that BMS never did anything to
16 attempt to characterize the structure of Impurities 1, 2,
17 3 and 6?

18 **A.** I'm not aware that they did. I'm not aware that they
19 didn't.

20 **Q.** And with respect to Impurity 5, BMS did engage in
21 work to try and characterize the structure of that,
22 correct?

23 **A.** It appears so.

24 **Q.** And is it your testimony that you think they got the
25 answer right or wrong?

~~Perni~~ - Cross

1 **A.** Based on Vanda's statement, my assumption is that
2 they got it right. But it's based strictly on Vanda's
3 document.

4 **Q.** You're not here separately offering an opinion that
5 BMS did, in fact, have possession of the correct structure
6 for Impurity 5; is that right?

7 **A.** I don't have data either way, so I'm relying strictly
8 on the Vanda document.

9 **Q.** And -- now, sometimes, even when you've got skilled
10 people working at this, is it not feasible to actually
11 identify the structure of an impurity?

12 **A.** Could you restate the question?

13 **Q.** Maybe I'll -- let's -- I'll try it a little
14 differently, all right?

15 **MR. GROOMBRIDGE:** Let's take that down,
16 Mr. Weir, and please put up the next paragraph which
17 begins with the words "the studies."

18 **BY MR. GROOMBRIDGE:**

19 **Q.** And this paragraph is talking about guidelines for
20 characterizing the structure of actual impurities?

21 **A.** Yes.

22 **Q.** And what the guideline is saying is that you should
23 go ahead and characterize the structure, correct?

24 **A.** Yes.

25 **Q.** But then it says: When identification of impurity is

~~Perni~~ - Cross

1 not feasible, a summary of laboratory studies
2 demonstrating the unsuccessful effort should be included
3 in the application.

4 **A.** Yes.

5 **Q.** Do you see that?

6 **A.** Yes.

7 **Q.** And would you agree that there are certainly
8 circumstances where it is not feasible to identify the
9 structure of an impurity?

10 **A.** It happens. I don't think it's particularly common,
11 but it happens.

12 **Q.** But there can be situations where it is quite
13 challenging as a technical matter?

14 **A.** Yes. Yes.

15 **Q.** It's not necessarily straightforward when you are
16 going through this process to figure out --

17 **A.** No.

18 **Q.** -- what is the correct chemical structure of the
19 impurity?

20 Sorry. I think you answered before I finished. For
21 the benefit of all concerned, let's -- I will try to
22 finish my question, and then if you wait until I've done
23 so and answer, that will be great.

24 And now, the -- if you can't identify the structure
25 of an impurity and it's present in amounts that could be

1 problematic, what would the guidelines tell you to do
2 about that?

3 **A.** Well, they want to see what you did to try to
4 identify -- they want to know exactly how hard you tried,
5 effectively.

6 **Q.** And if it's an impurity that could be -- could have
7 negative effects, could be poisonous, toxic, for example,
8 right, then the guidelines say you may have to end up
9 doing things, even perhaps clinical work, to figure out
10 that it's not a problem, right?

11 **A.** Correct.

12 **MR. GROOMBRIDGE:** And let's just go to the last
13 paragraph of this section, Mr. Weir.

14 **BY MR. GROOMBRIDGE:**

15 **Q.** And here, it's talking about potential impurities
16 that are expected to be unusually potent, producing toxic
17 or pharmaceutical effects at a level not more than the
18 identification threshold, and that would be 0.15 percent,
19 correct?

20 **A.** Yes.

21 **Q.** And would you agree that it is much, much easier to
22 figure out whether an impurity could have these dangerous
23 and undesirable effects if you know what it is?

24 **A.** Yes.

25 **MR. GROOMBRIDGE:** Thank you. That concludes my

1 questions.

2 **THE COURT:** All right. Any redirect?

3 REDIRECT EXAMINATION

4 **BY MS. WELLS:**

5 **Q.** Hi, Dr. Perni.

6 **A.** Hi.

7 **Q.** Do you recall that Mr. Groombridge was asking you
8 some questions about the '465 patent?

9 **A.** Yes.

10 **MS. WELLS:** Mr. Brooks, can you go ahead and
11 pull up JTX-6, and in particular I'd like to look at
12 Column 14, which follows right after that Schematic 5.
13 The very top of Column 14, blow that up for us.

14 **BY MS. WELLS:**

15 **Q.** Column 1 starts and says: In one example,
16 Intermediate 5 -- do you know what Intermediate 5 is
17 referring to?

18 **A.** Yes. I believe that's the carboxamide.

19 **Q.** Is it the carboxamide or the methanamine?

20 **A.** Isn't that following? Sorry. Let me look.

21 **MS. WELLS:** I think if you -- Mr. Brooks, may
22 we pull up Column 3, and right around Line 25. That might
23 be helpful.

24 **BY MS. WELLS:**

25 **Q.** You see where it says: The methanamine

1 Intermediate --

2 **A.** Yes. Sorry. I thought it was referring back to
3 the -- to Scheme 5.

4 **Q.** No problem. I know there's a lot of code names being
5 thrown around here.

6 **MS. WELLS:** Okay. Great. Let's take that
7 down.

8 **BY MS. WELLS:**

9 **Q.** Let's go back to the Column 14, the very top there
10 where it says: In one example, Intermediate 5 -- which is
11 the methanamine?

12 **A.** Yes.

13 **Q.** -- may be synthesized by the above scheme --
14 referring to Scheme 5.

15 Do you see that?

16 **A.** Yes.

17 **Q.** Does this language here in one example indicate to
18 you that there are other ways that you could make the
19 methanamine intermediate?

20 **A.** Yes.

21 **Q.** Did anything Mr. Groombridge asked you on cross, or
22 any of the answers that you gave on cross, alter your
23 opinions in this case?

24 **A.** No.

25 **Q.** Mr. Groombridge asked you a series of questions about

1 the disadvantages of putting a very strong reducing agent
2 together with a strong acid, like HCL.

3 Do you recall that?

4 **A.** Yes.

5 **Q.** And you agree that doing so could be detrimental,
6 could even lead to an explosion; is that right?

7 **A.** Yes.

8 **Q.** But are there other reducing agents that can be used
9 in the same reaction mixture with an acid and a
10 carboxamide to lead to methanamine?

11 **A.** Yes. There are reducing agents that can be combined
12 with what are typically considered not -- not strong acid,
13 but nevertheless are, in fact, acids that can be combined
14 in the presence of the carboxamide and you could obtain a
15 methanamine.

16 **Q.** So it's possible to carry out the reaction in Claim 1
17 of the '465 patent with other reducing agents and acids
18 mixed together with carboxamide to form the methanamine?

19 **A.** Yes.

20 **Q.** And you were also asked about whether the BMS process
21 was public knowledge.

22 Do you recall that?

23 **A.** Yes.

24 **Q.** Are you aware of any public disclosure that shows the
25 carboxamide to methanamine to tasimelteon synthesis from

1 BMS?

2 Any disclosure that BMS made public, not their -- not
3 the confidential IND?

4 **A.** The IND does become public at some point.

5 **Q.** Right. Do you know when the IND became public?

6 **A.** No, I do not.

7 **Q.** Are you aware of any publication from BMS that
8 discloses the carboxamide to methanamine to tasimelteon
9 process?

10 **A.** No, I'm not. I was assuming it was the IND.

11 **Q.** But you're not sure if or when the IND exactly became
12 public?

13 **A.** No.

14 **MS. WELLS:** And, Mr. Brooks, could we pull up
15 JTX-117, please.

16 **BY MS. WELLS:**

17 **Q.** Do you recall, Dr. Perni, that Mr. Groombridge asked
18 you about changes to BMS's manufacturing process?

19 **A.** Yes.

20 **MS. WELLS:** Mr. Brooks, could we do a
21 side-by-side of Scheme 1 on Page 6 and Scheme 3 on
22 Page 38, please. Is it possible to blow them, each, up a
23 little bit, just the schematic.

24 **BY MS. WELLS:**

25 **Q.** Do both schemes, Schematic 1 and Schematic 3 that BMS

1 was using involve going before a carboxamide to a
2 methanamine to tasimelteon?

3 **A.** Yes.

4 **Q.** Do they both involve reacting a carboxamide with a
5 reducing agent to form methanamine, followed by a step
6 where you react that methanamine with HCL and that gives
7 you the methanamine salt?

8 **A.** Yes.

9 **Q.** And do they both involve reacting that methanamine,
10 or methanamine salt, with a propionylating reagent to form
11 tasimelteon?

12 **A.** Yes.

13 **Q.** So for purposes of Claim 1 of the '465 patent, were
14 the changes that BMS made to the manufacturing process
15 material to whether that process --

16 **A.** No.

17 **Q.** -- claim?

18 **MS. WELLS:** No further questions.

19 **THE COURT:** Okay. I have a few questions. One
20 of them is similar to something Ms. Wells asked you.

21 So you recall Mr. Groombridge asked you a
22 number of questions about quenching in Column 14 of the
23 patent?

24 **THE WITNESS:** Yes.

25 **THE COURT:** And then he also asked you, after

1 that, some questions about basic chemistry.

2 **THE WITNESS:** Yes.

3 **THE COURT:** And then he asked you: Would you
4 also agree that in the reducing step, a person of ordinary
5 skill would know that if you put an acid in at that stage
6 in the presence of the reducing agents, it would, in
7 essence, prevent the reducing agent from doing its job?

8 And you answered: Correct.

9 He said: And that's a matter of basic
10 chemistry?

11 You said: Correct.

12 Are you saying there in general? Are you
13 saying there in the context of Column 14 or are you saying
14 something different?

15 **THE WITNESS:** I'm saying in the context of
16 Column 14.

17 **THE COURT:** And so that's what "at that stage"
18 is referring to it is something specific that was
19 discussed in Column 14.

20 **THE WITNESS:** Yes.

21 **THE COURT:** When you are discussing a chemical
22 reaction or transformation, what does "contact" mean?

23 **THE WITNESS:** To be honest, Your Honor, it is
24 not a term that chemists use. It is found in patents.

25 **THE COURT:** All right. But see, can we put up

1 the '465 patent please, Claim 1.

2 As a judge, right, I'm supposed to interpret
3 patents, and words of patents are supposed to have
4 meaning, right. They define important property rights.
5 And they define the meets and bounds of those property
6 rights, and every word is supposed to be given meaning as
7 a general proposition.

8 In the patent, Claim 1, in the '465 Patent
9 speaks of both contacting and reacting. And how would an
10 artisan or ordinary skill understand "contacting" in that
11 context?

12 **THE WITNESS:** Two molecules come together to
13 react.

14 **THE COURT:** They physically touch?

15 **THE WITNESS:** They physically touch.

16 **THE COURT:** That's different than -- the reason
17 why I asked, if you look at Column -- can we pull up
18 Column 6 of the patent?

19 Can we highlight the first big paragraph under
20 Column 6.

21 So in this sentence, as far as I can tell, in
22 every context "contacting" is used in the patent, it's
23 followed by the words "and reacting;" although, reacting
24 or reaction is used independent of contact.

25 But in this example, the first sentence says

1 that the synthesis you see of the VBF-INT-2 can comprise
2 contacting and reacting. Do you see that?

3 **THE WITNESS:** Yes.

4 **THE COURT:** Then it's followed, later on, if
5 you keep reading it, it gets to a comma. So you have a
6 contacting and reacting various chemicals in an organic
7 solvent. Do you see that?

8 **THE WITNESS:** Yes.

9 **THE COURT:** Then it says, comma, followed by
10 reacting. So that would suggest contacting reacting means
11 something different than reacting.

12 What's your understanding as an artisan of
13 ordinary skill how contacting reacting differs from
14 reacting?

15 **THE WITNESS:** It does not. I don't see any
16 physical way to distinguish the two. The reacting implies
17 that there is contacting.

18 **THE COURT:** Well, let's go back to Claim 1. If
19 I didn't have "contacting and" proceeding "reacting," and
20 I just had reacting the first chemical -- sorry. Let's
21 say it's reacting the carboxamide, right, we all agree
22 with that, right?

23 **THE WITNESS:** Yes.

24 **THE COURT:** Right. So the claim literally
25 reads, "contacting and reacting carboxamide with a

1 reducing agent and an acid in an organic solvent." So far
2 so good?

3 **THE WITNESS:** Yes.

4 **THE COURT:** Let's say I take away "contacting
5 and" and I just had "reacting carboxamide with a reducing
6 agent and an acid," if that's all it said, that could be
7 sequential or at the same time, right?

8 **THE WITNESS:** I would still read it at the same
9 time.

10 **THE COURT:** You still would?

11 **THE WITNESS:** I would.

12 **THE COURT:** But the thing is once you add
13 "contacting," that makes it different because it connotes
14 a physical --

15 **THE WITNESS:** Right.

16 **THE COURT:** Well, literally a contact.

17 **THE WITNESS:** You can have contact without a
18 reaction.

19 **THE COURT:** All right. It sounds like a lawyer
20 put "contacting" in as opposed to a chemist, doesn't it?

21 **THE WITNESS:** Yes, Your Honor.

22 **THE COURT:** That's a leading question, so I
23 will strike the answer.

24 All right. Thanks very much. You are excused.
25 Next.

1 (Witness excused.)

2 **MR. COBLENTZ:** Your Honor, it's after five.

3 Our next witness would be Dr. Emens, and we could call him
4 tomorrow.

5 **THE COURT:** What's -- is it a he or she?

6 **MR. COBLENTZ:** He.

7 **THE COURT:** What's he going to testify?

8 **MR. COBLENTZ:** Invalidity as the method of
9 treatment patents.

10 **THE COURT:** Is that it for your case?

11 **MR. COBLENTZ:** We have Dr. Greenblat, remember,
12 he will be coming on Thursday.

13 **THE COURT:** What was it exactly, I agreed
14 upfront that he could come Thursday? I don't remember
15 specifically. I remember trying to be accommodating.

16 What was the deal is he remote or wasn't
17 available?

18 **MR. COBLENTZ:** He is remote. He teaches, and
19 he couldn't get out of teaching obligations, so he will be
20 here.

21 **THE COURT:** He will be here. He is not going
22 to be remote.

23 **MR. COBLENTZ:** He will be here late in the
24 afternoon. You are thinking of another witness who is no
25 longer coming. That would be Dr. Grabowski. He is no

1 longer coming.

2 **THE COURT:** So he's coming late Thursday?

3 **MR. COBLENTZ:** No. He is coming late tomorrow.
4 So he won't be able to testify until Thursday morning. I
5 think the plan is --

6 **THE COURT:** You have two witnesses left?

7 **MR. COBLENTZ:** We have two witnesses left. I
8 think the plan is to have Dr. Emens.

9 **THE COURT:** How much time?

10 **MR. MILLIKEN:** Dr. Emens' direct examination
11 will be approximately an hour and 15 minutes.

12 **THE COURT:** Probably the other will be no more
13 than that too, right?

14 **MR. COBLENTZ:** That's right.

15 **THE COURT:** So that puts you about two more
16 hours. Ballpark it. You've taken less than seven. So
17 you are good. You will be way under 13 hours. Good.

18 Mr. Groombridge, what do you have left?

19 **MR. GROOMBRIDGE:** I will defer to Mr. Stone
20 because he's more up on this.

21 **MR. STONE:** We have four witnesses left. We
22 will call two of them tomorrow, Dr. Bergmeier again on the
23 manufacturing patent and invalidity and then that's done.
24 Dr. Lockley, who will be testifying in rebuttal on
25 invalidity of the method of treatment patents.

1 We then need to wait until Dr. Greenblat is
2 done so we can call Dr. Czeisler, and, forgive me, Dr.
3 Parkinson in response to Dr. Greenblatt.

4 We will easily get all of that done Thursday if
5 the length of time they are proposing is what they say it
6 is going to be.

7 **THE COURT:** We will finish Thursday by ten in
8 the morning sounds to me.

9 **MR. STONE:** Three witnesses on Thursday, I
10 don't think we're finishing by the 10:00 in the morning.

11 **THE COURT:** We will definitely finish before
12 lunch.

13 What are these people you're calling going to
14 talk about in rebuttal; what are the issues?

15 **MR. STONE:** So the manufacturing patent is,
16 basically, why our witness disagrees.

17 **THE COURT:** That's the fellow coming tomorrow?

18 **MR. STONE:** You mean the Thursday witness?

19 Let me start, if I may, with what I think Dr.
20 Greenblatt is going to tell the Court.

21 I think Dr. Greenblatt is going to tell the
22 Court that a patent on a drug-drug interaction is obvious.
23 You have to figure out whether there are drug-drug
24 interactions. There was enough known in the art that
25 would have caused a skilled artisan to want to not combine

1 tasimelteon with these CYP inhibitors.

2 Dr. Parkinson is going to respond to that from
3 the perspective of drug-drug interaction science, which is
4 his area.

5 And then Dr. Czeisler is going to respond to
6 that, in part, depending on how much of Dr. Greenblatt's
7 testimony touches the method of treatment part and how
8 much touches the drug-drug interaction part.

9 And Dr. Czeisler is also going to respond in
10 part to their next witness, Dr. Emens on invalidity on,
11 you know, why is this reference not teach the claim, why
12 is this obvious combination not -- he is one of our core
13 obviousness experts.

14 **THE COURT:** Okay. Is this a case you want to
15 do closing arguments on Friday morning or, no, I'm
16 confused?

17 **MR. ROZENDAAL:** It would be an act of kindness
18 to put them on Friday, Your Honor.

19 **MR. COBLENTZ:** One thing I want to mention is
20 Dr. Czeisler is bringing -- if you are bringing secondary
21 considerations with Dr. Czeisler, we might have a short
22 rebuttal with Dr. Emens. It would be very short on
23 Thursday afternoon.

24 **THE COURT:** What are the secondary
25 considerations you are talking about?

1 **MR. STONE:** Long-felt need, we may be talking
2 about failure of others. To be perfectly honest with you,
3 Your Honor, we can confer to make sure --

4 **THE COURT:** I'm just curious. I don't mind you
5 proffering.

6 What's the long-felt need for? How many -- we
7 don't know how many patients in the world there are --

8 **MR. STONE:** I think Your Honor heard earlier is
9 wrong. We don't know how many there are. It is an order
10 of magnitude more than that.

11 So I think some of the evidence is going to be
12 about prevalence. I think the Court is also going to hear
13 that they are not all blind. There are sighted people
14 that's in the diagnostic manual. A lot of what Your Honor
15 heard today is incorrect. Granted, it is not one person
16 on every block in America.

17 **THE COURT:** How much off-label use does this
18 drug get?

19 **MR. STONE:** I don't know that I know the answer
20 to that question.

21 **MR. GROOMBRIDGE:** As far as we know, none. I
22 don't know that we've ever drilled into that, but --

23 **THE COURT:** I'm asking. This is all attorneys.
24 I am not holding you to it.

25 Sometimes you wonder, like, you know, what's

1 really driving the train in these cases. I tell my
2 clerks -- this is for all the business people, the
3 in-house people -- that you have to accept that the
4 attorneys don't appear to always be acting rationally
5 because we're just one little battle in a much larger war.

6 So the actors may be acting rationally when you
7 view the whole war, but in our particular case, when they
8 seem to be acting irrationally, which happens,
9 unfortunately, often -- not that it's happening here, but
10 there actually may be a reason to it. It's just that
11 we're only privy to the battle, not the war.

12 That's why I wondered in this. Is there
13 off-label use driving this train that I don't know about?

14 **MR. GROOMBRIDGE:** Not to my knowledge, Your
15 Honor.

16 And in case it's helpful to the Court, people
17 may differ. In terms of order of magnitude, the reissue
18 patent at the beginning when it talks about Non-24, talks
19 about how many, what the patient population is, and
20 it's --

21 **THE COURT:** In fairness to the doctor because I
22 hit him cold on it, but I mean my recollection of the
23 testimony was that it was basically like not fully blind.
24 There was something about that argument. I remember light
25 deprived or something has to do with, but it is

1 effectively people who are blind, I thought.

2 **MR. STONE:** It is primarily people who are
3 blind is what Your Honor is remembering. That's certainly
4 true.

5 To the point that the doctor was making, when
6 you have a patient come into clinic, who can see, but
7 their circadian rhythm keeps drifting, given
8 definitionally the drifting circadian rhythm like that is
9 Non-24. There actually is a meaningful amount of sighted
10 people who have Non-24. It is certainly primarily blind.

11 **THE COURT:** Okay. Ms. Wells, question for you.

12 So the expert that you did the direct of had
13 basically what I call three obvious -- no, it was two.

14 So the BMS patent, coupled with the ICH and
15 Chinese patent coupled with the ICH.

16 And this comes up in all these cases. I don't
17 think I've ever asked someone this. You are the guinea
18 pig.

19 So why isn't it, three, the Chinese patent, the
20 '529 and the ICH?

21 **MS. WELLS:** Combination with all three?

22 **THE COURT:** Uh-huh.

23 **MS. WELLS:** I suppose you could. I don't
24 think -- I think each sort of stand on its own. So you
25 can just with the Chinese patent application and ICH

1 Guidelines, that combination we're arguing renders it
2 obviously. That's separate and apart from the second
3 ground, which also independently renders it obviously.

4 **THE COURT:** Isn't there a third ground, all
5 three? No.

6 **MS. WELLS:** I mean, to be frank, we agreed, as
7 part of the case narrowing, to limit the amount of
8 invalidity grounds to three per claim. So we went with
9 what we thought were our strongest.

10 **THE COURT:** I have no comment. My question
11 doesn't go to the strength of the argument at all.

12 My question just goes to even when you all
13 limit it in cases, which we do require, it struck me
14 that -- part of the reason I also ask is because I had to
15 deal with an issue once where there were multiple
16 references, numerous references, and then they dropped it
17 to one reference, and the plaintiff complained. I was
18 trying to find it hard to understand that, but anyway,
19 okay.

20 So you just separate the two, all right.

21 All right. Well, so then, in terms of planning
22 for the rest of the trial, we've got two witnesses
23 tomorrow. That's a half day.

24 **MR. ROZENDAAL:** Three.

25 **MR. COBLENTZ:** Three. It would be Greenblat,

1 Dr. Greenblat.

2 **MR. ROZENDAAL:** Tomorrow is Dr. Emens, Dr.
3 Bergmeier and Dr. Lockley.

4 **THE COURT:** Okay. And at most, three on
5 Thursday.

6 **MR. STONE:** It will be three on Thursday, but,
7 yes, three each day.

8 **THE COURT:** You are calling them?

9 **MR. COBLENTZ:** Possibly Dr. Emens to rebut the
10 secondary considerations.

11 **THE COURT:** That's right. Mr. Milliken said
12 that.

13 **MR. MILLIKEN:** Just to clarify, Your Honor, by
14 "short," we mean, less than five minutes.

15 **THE COURT:** Okay. So how much time are we
16 going tomorrow?

17 **MR. GROOMBRIDGE:** For Dr. Emens, I think I
18 heard counsel say about an hour, 15 for the direct, and
19 I'm anticipating the cross would be 45 minutes or so.

20 **THE COURT:** And then what's after that?

21 **MS. YOUNG:** Will be about 30 minutes on direct
22 examination.

23 **THE COURT:** And then who is the third witness?

24 **MR. GROOMBRIDGE:** That's Dr. Lockley, I think
25 the direct is likely to be, let's say, 45 minutes to not

1 err on the side of too --

2 **THE COURT:** All right. I think we should be
3 done by lunch tomorrow. That's what I'm going to shoot
4 for, certainly very early in the afternoon.

5 You asked for acts of kindness. Given you are
6 going to have Wednesday afternoon off, I'm thinking why
7 don't we finish this up on Thursday.

8 We have to do claim construction. That's the
9 other thing. I mean, maybe we should do claim
10 construction tomorrow afternoon then on the '465 patent.

11 What do you think the claim means,
12 Mr. Groombridge? What do I need to construe? You don't
13 think I need to construe anything. If I don't construe
14 anything, what does "contacting" mean?

15 **MR. GROOMBRIDGE:** I think, it had been our
16 sense it had plain and ordinary meaning. I think we need
17 to put all the pieces together because this is an issue
18 that has coalesced in the last two days.

19 **THE COURT:** By the way, I was never asked to
20 construe "contacting" or "reacting" before.

21 **MR. GROOMBRIDGE:** Correct, correct.

22 **THE COURT:** Okay.

23 **MR. GROOMBRIDGE:** So I think what we'd like to
24 do --

25 **THE COURT:** Probably because you said it has

1 plain and ordinary meaning.

2 **MR. GROOMBRIDGE:** Not clear to me that the
3 part --

4 **THE COURT:** What I'm getting at, because you
5 said it hasn't been crystalized, in fairness to the
6 defense, you are the plaintiff. If you didn't think it
7 needed to be construed, if I am a defendant, I am reading
8 this.

9 If I'm just reading this, it has to be
10 contacting and reacting carboxamide with a reducing agent
11 and an acid, has to be with both. The "with" a reducing
12 agent and acid are the objects that follow the "with;" you
13 agree with that.

14 **MR. GROOMBRIDGE:** Yes.

15 **THE COURT:** It's done in an organic solvent and
16 it says "contacting." It has to be with both.

17 **MR. GROOMBRIDGE:** Our view of the world, it
18 doesn't require though that they be simultaneous, and that
19 what the skilled person would understand because when you
20 read -- as the testimony was, when you read this, you
21 understand that this is how the chemistry would work. And
22 that you would do the reduction and then the acid, if you
23 put the acid in with the reduction, so a skilled person
24 would know that, and would say this is kind of the
25 shorthand for what's described in the example. And that's

1 how it's always done.

2 So in our thinking, that was the plain and
3 ordinary meaning. In other words, a skilled chemist
4 looking at this would say, I get it; I see what this is
5 talking about, it's that. Rather than viewing it as
6 lawyers might, as a grammarian, right.

7 I mean, I think that was, the level of the --
8 wasn't as though we are saying we are proposing a
9 construction at this point.

10 **THE COURT:** Let's step back. It is a factual
11 matter the Teva and Apotex composition when it's created,
12 you've got carboxamide, right?

13 **MR. ROZENDAAL:** Yes. There's a process step
14 with the carboxamide. Yes.

15 **THE COURT:** It is in a vessel?

16 **MR. ROZENDAAL:** I would imagine so, yes, in a
17 solution of some sort. Yes.

18 **THE COURT:** How big is the tank?

19 You know, I'd love to know. And then is it
20 poured in to some other vessel in which there's a solvent?
21 I mean --

22 **MR. LUKAS:** At least for Apotex, Your Honor,
23 the first reaction takes place, reducing reaction. Same
24 vessel, more, you know, then the acid, that reaction is
25 done.

1 **THE COURT:** Step back. Like someone is in a
2 factory, drive in. Somebody takes a bucket of
3 carboxamide, they pour it into something?

4 **MR. LUKAS:** It's an organic solvent.

5 **THE COURT:** And they pour it into an organic
6 solvent?

7 **MR. LUKAS:** It's being mixed up, reacts with
8 reducing agent.

9 **THE COURT:** They separately pour in a reducing
10 agent?

11 **MR. LUKAS:** It is added, yes. It's added to
12 react with the carboxamide.

13 **THE COURT:** And the solvent, they are in
14 together or is it, first, they've got the carboxamide,
15 then they pour in the reagent, and then they pour in the
16 solvent?

17 **MR. LUKAS:** No. That's not how it works. The
18 solvent has to be there.

19 **THE COURT:** Solvent is there the whole time?

20 **MR. LUKAS:** It is there to let the things that
21 need to react with each other to come in contact with each
22 other.

23 **THE COURT:** So you pour in the carboxamide.
24 Now, you pour in the agent, and then do you pour the acid
25 in?

1 **MR. LUKAS:** After that first reaction is done.

2 **THE COURT:** Right. But the solvent, all of it
3 in that solvent?

4 **MR. LUKAS:** Yep.

5 **THE COURT:** Okay.

6 **MR. GROOMBRIDGE:** Your Honor, I think we would
7 be happy to do the claim construction tomorrow afternoon,
8 if that suits the Court.

9 **THE COURT:** All right. So why don't we plan on
10 it. Be prepared to do the claim construction, and I'll
11 construe it.

12 And the cases, let's make sure -- the cookie
13 case is what again?

14 **MR. ROZENDAAL:** It is *Chef America versus Lamb*
15 *Weston*, and we do not have the Federal Circuit cite, but
16 Your Honor gives me a moment, I'm happy to pull it up.

17 **THE COURT:** Your favorite case?

18 **MR. GROOMBRIDGE:** My favorite case is called
19 Vanda. I will have the cite for you in a just a moment.

20 **MR. STONE:** Cookie case, you are stuck with the
21 language of your claim, the cookie case being --

22 **THE COURT:** Right. Either that -- yes. I
23 mean, if you want your favorite case on that topic or
24 favorite case, whatever you want.

25 **MR. STONE:** That's not --

1 **MR. GROOMBRIDGE:** There's a body of case law
2 about when you can and can't read out the preferred
3 embodiments. That's one of the things we're focused on.

4 I don't have a citation for Your Honor at the
5 moment. We will certainly have that by tomorrow.

6 **MR. ROZENDAAL:** I believe the citation for Chef
7 America, Your Honor, is 358 F.3d 1371, and that would be
8 Federal Circuit 2004.

9 **THE COURT:** Okay. All right. We will see you
10 tomorrow at 8:30.

11 Anything else anything I need to resolve
12 tonight?

13 **MR. ROZENDAAL:** No.

14 **THE COURT:** We didn't figure out about closing
15 arguments. I think, I'm not sure how helpful it's going
16 to be. I think it might be helpful to not have closing
17 arguments and have briefing.

18 The only thing is this claim construction
19 issue. I want to resolve that this week, and I think it
20 will help the briefing.

21 **MR. ROZENDAAL:** I think if Your Honor wanted to
22 either not have argument or wanted to have argument after
23 you've seen the briefing --

24 **THE COURT:** That's what I'm talking about. We
25 could do that maybe.

1 **MR. ROZENDAAL:** That would be, I think, fine
2 with us. I would say if you change your mind and decide
3 you want the arguments now, I would suggest the quality of
4 arguments you get will be better on Friday than on
5 Thursday.

6 **THE COURT:** I am aware of that. I am also
7 aware -- here's my problem is you guys will fill the time.
8 So like if I don't cut it off, then we are here Thursday
9 afternoon.

10 I have other work to do. That's why I'm
11 really, you know, if you said we will be done by lunch
12 tomorrow, be done by lunch Thursday, come back for oral
13 arguments on Friday.

14 But you are not doing that, so I know it's
15 going to happen, and I gave way too much time because
16 already. We're largely done, and you are both about
17 seven-ish, you're well under the time.

18 So I don't want to give you Friday morning
19 because of that. I have other things I have to get done.
20 So you can think about it.

21 Tomorrow we will plan on getting through those
22 three witnesses and do claim construction for sure, and
23 then we will see what's left.

24 And if you have come across a case or you have
25 a piece of prosecution history, you want me to look at,

1 you can file it. We will look at it. I come in early in
2 the morning, and we can start looking at it in preparation
3 for the argument. Think about that too. All right.

4 I will see you tomorrow.

5 **MR. STONE:** I understood the Court to have said
6 earlier with respect to claim construction, the Court
7 didn't want briefing.

8 **THE COURT:** I don't want briefing. I am
9 talking about if you are going to come in tomorrow and say
10 to me, guess what to get this thing patented, they had to
11 inject the word contacting or get, you know something like
12 that.

13 In other words, I get the principle about you
14 generally don't read out embodiments. I get that. I get
15 the bigger principle that the claims defined meets the
16 bounds of the patent.

17 **MR. STONE:** Understood, Your Honor.

18 **THE COURT:** Those are principles I don't need
19 case law. I can do that with that.

20 The question, is there any other intrinsic
21 evidence that helps either side. You should get that to
22 my attention, and I've got a chemist, who was pretty
23 credible, who said "contact" doesn't mean anything. It is
24 a lawyer's words.

25 You know what, I am a big believer that clients

1 that people who get a patent, they ought to bare the
2 consequences when their lawyers put word in the claims of
3 patents.

4 That is one thing I really believe strongly in
5 because I am a big proponent of patent rights, but I'm
6 also a big proponent that people shouldn't be able to take
7 advantage of patents to stop innovation.

8 So that's where I am. All right. I believe
9 strongly about those principles.

10 All right. See you tomorrow morning at 8:30.

11
12 (The proceedings concluded at 5:24 p.m.)
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CERTIFICATE OF COURT REPORTER

I hereby certify that the foregoing is a true and accurate transcript from my stenographic notes in the proceeding.

/s/ Bonnie R. Archer
Bonnie R. Archer, RPR
Official Court Reporter
U. S. District Court

<p>BY MR. COBLENTZ: [23] 492/11 492/22 493/5 494/20 497/17 498/8 499/2 499/12 502/3 503/2 505/12 506/6 508/2 511/12 511/22 512/17 512/25 513/18 519/25 521/21 522/1 522/16 550/6 BY MR. GROOMBRIDGE: [18] 616/10 616/20 617/22 620/9 620/24 621/20 622/6 626/16 627/6 629/5 631/20 632/5 633/16 636/7 637/11 637/19 640/18 642/14 BY MR. KLEIN: [14] 524/4 526/5 527/21 531/24 532/10 533/20 536/11 538/8 538/22 541/16 542/19 544/11 544/23 545/3 BY MR. LUKAS: [23] 396/4 396/14 397/1 399/11 401/6 402/12 403/9 407/5 407/16 410/7 412/12 414/9 415/7 415/15 416/17 418/14 419/24 420/21 421/8 421/25 460/24 462/17 462/25 BY MR. ROZENDAAL: [2] 374/23 376/5 BY MR. STONE: [23] 424/6 430/3 430/22 433/6 437/7 437/19 440/23 441/12 442/9 443/4 446/8 447/18 447/25 448/21 450/1 451/16 452/14 452/22 453/21 455/6 455/16 456/15 456/20 BY MS. WELLS: [18] 577/14 577/25 578/17 587/25 589/3 590/22 592/12 603/24 605/4 608/24 610/5 611/8 643/4 643/14 643/24 644/8 646/16 646/24 BY MS. 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<p>0.15 percent... [12] 612/1 612/4 612/10 612/18 612/20 615/13 615/16 615/22 632/14 638/15 638/17 642/18 0.44 percent [1] 632/25 0.5 MGS [1] 469/25 0.5 milligrams [1] 470/2 00019621 [1] 471/24 004 [2] 629/13 631/25 006 [3] 336/14 336/16 371/22 007 [1] 631/21 00808260 [1] 563/15 01101260 [1] 563/4 02 Micro [1] 369/16 02021394 [1] 469/1 02021397 [1] 469/3 02021407 [1] 469/5 02456066 [1] 467/16 028 [1] 531/18 030 [6] 538/1 538/5 541/9 541/13 544/6 544/8 06 [1] 336/21 094 [5] 333/20 344/21 345/6 345/9 345/13</p>	<p>13 [12] 371/22 372/6 417/3 512/24 513/8 513/12 550/20 599/16 599/17 616/19 617/1 653/17 132 [3] 519/24 548/18 548/20 132.11 [1] 520/11 1371 [2] 393/19 666/7 139 [7] 419/15 419/18 419/23 420/18 456/8 456/14 456/23 13th [1] 406/22 14 [22] 384/7 420/6 420/11 420/12 422/6 436/24 473/18 542/23 592/11 619/23 619/24 620/20 620/23 621/19 621/25 643/12 643/13 644/9 647/22 648/13 648/16 648/19 14.1 [2] 503/3 503/24 140 [1] 398/12 146 [1] 453/13 15 [9] 347/10 514/18 562/10 570/20 617/3 620/7 628/24 653/11 660/18 15 minutes [3] 463/21 464/3 464/4 150 [2] 453/17 453/20 151 [1] 453/20 16 [1] 348/3 16 years [1] 628/24 1621111 [1] 484/18 1623201 [2] 468/14 468/17 164 [3] 432/22 433/2 433/5 17 [2] 526/4 526/6 17.5 percent [1] 510/8 17th [1] 575/19 18 [9] 339/25 359/8 362/22 363/1 363/2 366/7 405/16 406/16 485/8 18-651-CFC [1] 1/5 185 [2] 505/18 506/5 188 [2] 526/4 526/7 19 [3] 352/2 506/12 636/14 190 fold [1] 486/1 193 [4] 542/16 542/17 542/20 542/22 194 [2] 542/23 542/23 195 [2] 514/17 515/2 1986 [1] 397/14 1989 [1] 397/16 1990s [3] 625/5 631/2 634/10 1997 [3] 575/19 593/18 593/20 1998 [5] 563/1 594/3 594/4 596/9 598/5 1999 [3] 594/9 594/11 613/10 1:00 work [1] 481/6 1:30 a.m [1] 490/7 1A [4] 509/11 509/15 509/17 509/18 1A2 [2] 485/23 485/25 1A2's [1] 485/1 1B [4] 509/11 509/17 510/4 510/7</p>	<p>2.6 [2] 421/7 510/9 2.6 percent [1] 509/22 20 [4] 542/17 542/22 564/20 576/6 20 milligrams [3] 474/10 482/17 526/16 20 percent [2] 466/14 510/18 20-milligram [1] 485/21 20.0 percent [1] 509/20 2000 [3] 332/12 472/11 472/11 2004 [6] 393/20 566/10 594/12 594/13 633/18 666/8 2005 [1] 561/19 2006 [4] 559/17 594/20 594/22 604/1 2008 [3] 482/12 482/16 482/20 2009 [1] 488/13 2010 [5] 478/22 483/6 483/17 483/18 483/25 2011 [6] 402/17 405/10 405/16 406/1 406/16 579/19 2012 [10] 409/15 412/2 413/11 449/20 451/2 472/6 594/23 594/24 609/1 636/14 2013 [6] 413/21 413/23 436/24 568/19 568/21 568/25 2014 [13] 413/24 416/5 586/23 587/10 594/25 595/1 595/6 604/2 609/2 612/8 613/11 613/15 615/19 2017 [1] 388/25 2019 [6] 351/22 352/12 353/2 353/11 354/8 355/19 2020 [5] 352/2 353/15 353/24 353/25 368/8 2021 [2] 333/15 339/24 2022 [1] 1/10 21 [1] 360/16 21 CFR 314 [1] 410/9 2101 [1] 483/18 214778 [1] 467/20 22 [4] 356/10 356/14 466/7 536/10 22 minutes [2] 500/15 500/17 23 [1] 416/5 233 [4] 447/2 447/7 447/10 447/15 24 [94] 418/17 439/2 443/24 458/13 459/19 460/8 466/19 466/24 468/15 468/21 469/18 471/20 473/20 474/9 487/5 487/12 487/18 488/23 489/1 490/13 496/7 496/12 496/19 496/20 496/21 498/13 498/16 498/19 500/7 501/12 501/16 503/12 514/1 515/23 516/8 516/12 516/16 519/21 521/3 521/17 524/9 524/12 524/16 525/3 525/14 526/10 528/4 528/8 528/12 528/15 528/21 529/1 529/8 529/10 529/21 529/24 531/8 532/18 533/4 533/4 533/7 535/2 535/16 535/18 535/20 536/13 536/15 537/4 537/8 537/16 537/22 539/1 540/5 540/19 541/7 545/18 552/22 553/14 553/17 553/18 553/23 554/3 554/6</p>	<p>554/21 557/6 563/3 564/4 564/8 576/11 636/3 636/4 657/18 658/9 658/10 24-hour [4] 457/5 529/13 529/19 543/10 245 [1] 515/3 25 [8] 491/13 491/16 520/9 526/4 526/7 557/22 617/3 643/22 25 percent [13] 411/22 411/23 465/1 500/14 508/10 514/19 514/21 533/25 534/8 534/9 534/12 534/15 534/18 26 [3] 520/6 563/14 565/1 263 [6] 440/5 440/19 440/22 443/6 461/11 463/2 27 [3] 339/24 622/5 622/7 270 [1] 329/22 271 [1] 329/22 2724 [1] 575/11 27th [1] 561/19 28 [13] 360/16 363/10 363/14 418/5 494/23 496/1 498/18 499/3 499/25 502/5 503/1 514/13 532/4 283 [1] 485/9 28th [1] 451/2 29 [2] 1/10 360/16</p>
<p>1 1.4 [1] 628/6 1.48 [1] 625/19 1.5 [1] 628/2 1.50 [1] 625/19 10 [42] 331/9 336/19 336/22 337/1 338/24 339/5 340/22 341/1 341/10 341/16 342/2 345/25 346/6 346/12 347/21 348/5 348/12 348/16 351/22 360/20 361/2 370/13 373/25 374/6 374/9 384/8 395/15 397/5 488/3 488/5 538/3 538/5 544/9 581/15 581/16 588/5 589/25 608/11 613/4 613/7 616/1 627/3 10 milligrams [1] 469/24 10,000 [1] 553/1 1042 [1] 478/21 10:00 [1] 654/10 11 [1] 345/15 110 [11] 414/1 414/8 436/6 437/6 452/4 452/12 452/20 453/13 570/20 570/20 570/20 1117 [1] 388/1 114 [4] 468/25 469/2 469/4 469/6 115 [2] 469/1 469/14 116 [2] 469/3 469/14 117 [7] 595/22 595/24 596/6 597/24 628/24 631/18 646/15 117-page [1] 447/20 12 [7] 346/4 456/13 456/23 503/3 597/24 605/6 614/9 120 [1] 481/1 121 [1] 471/23 124 [1] 473/16 1244 [1] 564/8 128 [2] 521/20 522/7 128.42 [1] 522/17 129 [3] 521/25 522/9 522/13 129.9 [1] 522/18 12th [1] 488/13</p>	<p>2 2.1 [1] 399/10 2.2 [1] 401/4 2.3 [6] 402/11 405/10 409/14 411/25 413/20 416/4 2.4 [1] 415/14 2.5 [2] 420/20 421/24</p>	<p>2 2.1 [1] 399/10 2.2 [1] 401/4 2.3 [6] 402/11 405/10 409/14 411/25 413/20 416/4 2.4 [1] 415/14 2.5 [2] 420/20 421/24</p>	<p>3 3 III [1] 413/1 3.10 [1] 502/2 3.11 [1] 505/1 3.12 [1] 506/7 3.13 [2] 509/5 509/7 3.15 [2] 511/6 511/11 3.16 [2] 511/10 511/21 3.17 [1] 512/16 3.18 [1] 513/19 3.19 [2] 514/11 533/18 3.2 [1] 494/21 3.20 [1] 516/1 3.21 [2] 516/21 517/11 3.23 [1] 518/15 3.24 [1] 519/13 3.26 [1] 520/19 3.27 [1] 521/5 3.28 [1] 522/15 3.3 [1] 495/16 3.3 hours [1] 465/1 3.4 [1] 495/25 3.6 [1] 497/18 3.7 [1] 498/7 3.8 [2] 498/17 499/3 3.9 [1] 499/11 30 [10] 423/8 494/25 550/12 550/13 550/18 551/20 605/3 605/5 617/2 660/21 30 minutes [1] 482/18 30 years [2] 411/12 494/12 30-minute [1] 481/15 30-plus [1] 392/16 301 [5] 608/15 608/17 608/19 608/23 636/2 31 [1] 481/1 31.6 percent [1] 510/13 3101 [1] 483/19 314 [1] 410/9 32 [1] 372/6 3201 [12] 403/21 404/1 404/3</p>

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